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THE CONTROL OF SUPPLEMENTAL OXYGEN BY OXIMETRY*

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THE NEWBORN PREMATURE INFANT in respiratory distress is menaced by two dangers. Firstly, there is the danger of damage to vital centres entailed in hypoxia.[1] Secondly there is the possibility of retrolental fibroplasia following on an unnecessarily high partial pressure of oxygen in arterial blood (PaO_2) from unduly high and long continued inspired oxygen concentrations.[2–10] A control method is therefore required to ensure that inspired oxygen concentration conforms to the requirement of the infant.

This paper describes experience in the control of supplemental oxygen by a diamagnetic oxygen analyser and a Wood ear oximeter. The investigation was aimed primarily at establishing the feasibility of the method. No specific weight group was observed and no attempt is made to draw statistical conclusions from the series, since the numbers involved are too small. However, some observations on the required duration of therapy and concentrations of oxygen have been made and will be discussed.

Apparatus

The Wood ear oximeter registers photo-electrically the transmission of light in the visible red (640 millimicrons) and near infra-red (800 millimicrons) wave bands by blood in the heat-flushed ear with varying relative percentages of oxyhæmoglobin and total hæmoglobin.[11] The ratio of transmission in the visible red to that in the infra-red is a function of the arterial oxygen saturation (SaO_2). By bucking output of the two photocells of the earpiece against each other a continuous reading of arterial oxygen saturation is obtained which has been shown to be within 5% of simultaneous samples of arterial blood analyzed by the van Slyke technique.[11–13] It is important for accuracy that the peripheral circulation through the ear be adequate and the capillary blood fully arterialized in the pinna by heat generated from the earpiece light source. Below 75% arterial saturation the error of the method increases progressively to reach a standard deviation from the mean of the order of 10% from simultaneous van Slyke analyses at an arterial oxygen saturation of 60%.

The diamagnetic oxygen analyser is now standard equipment and need not be discussed further. The model used had an accuracy of plus or minus 1%.*

Method

The earpiece is applied to the infant's ear while in the isolette and the effect of varying atmospheric oxygen concentration within the isolette on arterial oxygen saturation is recorded. The least concentration of oxygen that will maintain a normal 95-98% arterial saturation is found by trial. Serial daily observations are made as far as possible, until it is found that the infant maintains a normal arterial oxygen saturation in air.

RESULTS

The 31 patients investigated were receiving supplemental oxygen on clinical grounds without prior knowledge of the oximetry results. The indications for oxygen were cyanosis of presumed central origin or dyspnœa or both.

TABLE I.—INITIAL ARTERIAL OXYGEN SATURATIONS IN 15 DESATURATED CASES WITH THE REQUIRED MINIMUM INSPIRED OXYGEN LEVELS FOR NORMAL SATURATION.

Case	*% Arterial oxygen saturation at first, examined in air unless otherwise stated*	*Required O_2 concentration % to raise arterial O_2 saturation to 95%*
Wi.	67 in 27% O_2	59 for 89% SaO_2
Al.	51	59
Br.	<63	50
Re.	88 in 29%	48
St.	50	42 for 92% SaO_2
Wa.	89.5	31
Vi.	83	30
Wis.	81.5	30
An.	91	29
To.	84	28
Bro.	81	27
Gl.	87.5	26
Pe.	88	26
Sc.	<40	Not known

In 14 patients receiving supplemental oxygen on clinical grounds, arterial oxygen saturations were above 95% when they were removed from oxygen and tested in air. However, none of these

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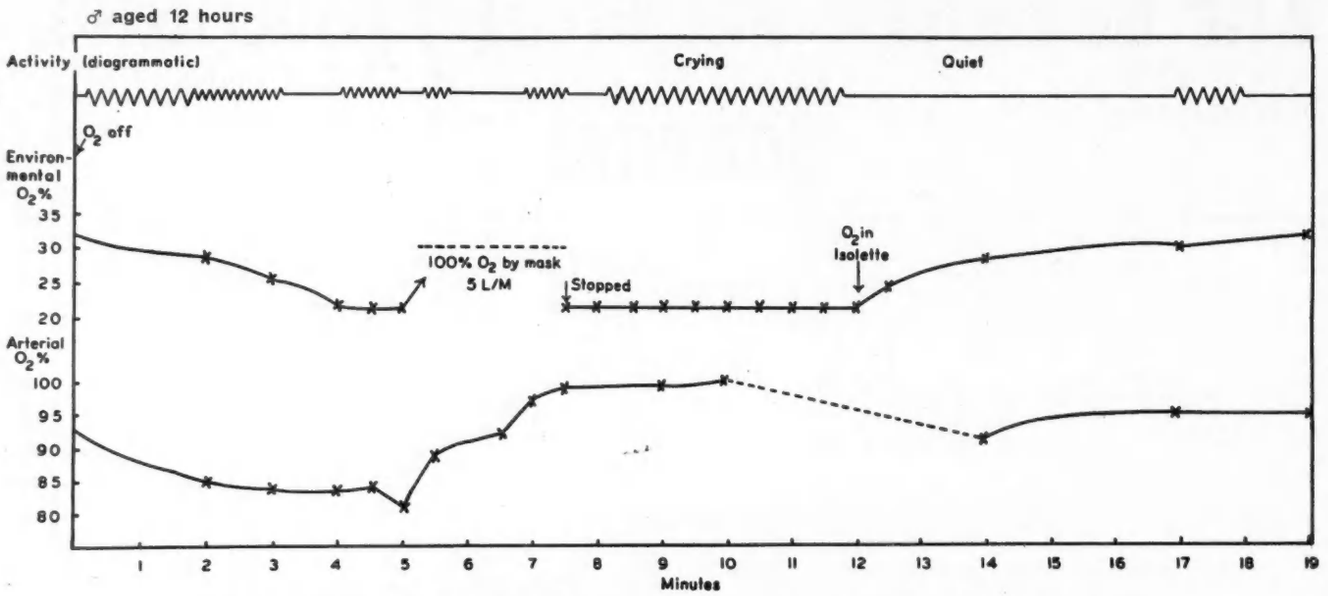

Fig. 1.—Birth weight 5 lb. 2 oz. The effect of supplemental oxygen on SaO_2. Note that at the end of the record a normal SaO_2 is maintained with approximately 30% ambient O_2.

infants had a birth weight of under 4 lb. and none was receiving over 35% oxygen. These infants were therefore unlikely candidates for retrolental fibroplasia, but were probably receiving oxygen unnecessarily. Two infants were moribund and in profound peripheral circulatory failure. Under these circumstances the circulation through the ear did not become arterialized in response to the heat of the earpiece light source. The method is therefore useless in such cases.

In one case, the blood was desaturated in air at the first examination, but the required level of oxygen for normal saturation could not be determined owing to technical difficulties. However, this patient achieved 89% saturation with 59% supplemental oxygen.

In 14 cases there was less than 95% saturation at their first examination. Table I gives the arterial oxygen saturation at the first examination and the percentage concentration of supplemental oxygen required (see also Fig. 6). The figures show that a significant proportion of cases required more than 40% oxygen initially to achieve an approximately normal arterial oxygen saturation (six out of 15). Five died, though in one the cause of death was unrelated to respiratory failure. With one exception, which will be discussed later, no surviving infant required supplemental oxygen for

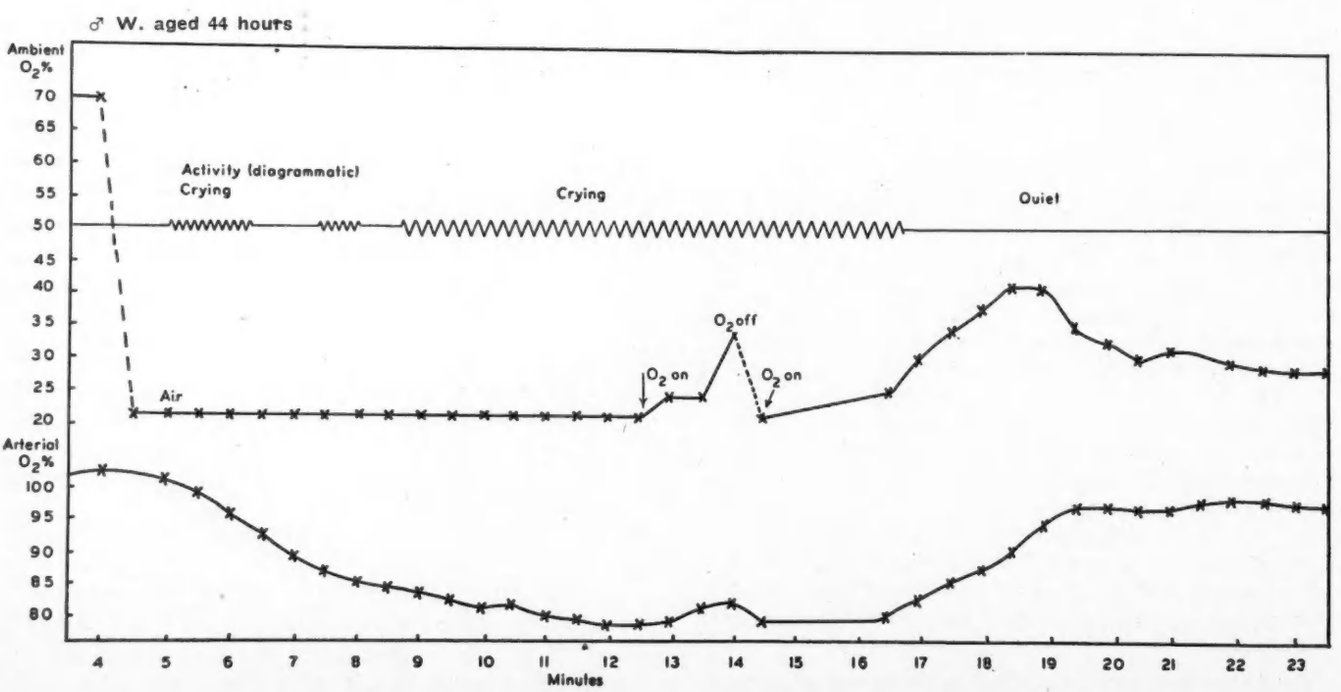

Fig. 2.—The same infant at 44 hours still shows arterial desaturation breathing air, but SaO_2 is again restored to normal by 30% O_2 at the end of the record.

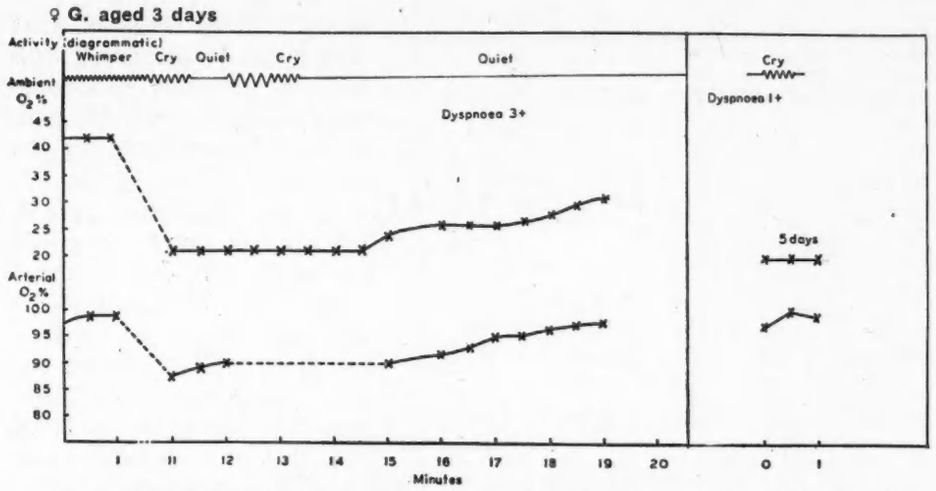

Fig. 3.—This infant shows arterial oxygen desaturation on the third day when placed in air, but normal saturation in air on the fifth day.

longer than five days. The tendency was for the requirement for supplemental oxygen to diminish progressively with the passage of time (Fig 7).

One infant requiring oxygen for longer than five days was proven by angiocardiography on the second day of life to have a persistent patency of the ductus arteriosus with reversal of flow. This infant had a lower arterial oxygen saturation with the earpiece on the scrotum than was registered with the earpiece on the ear during the first eight days of life. The degree of desaturation on the ear was not clinically significant after eight days. Further examination at two months disclosed a normal arterial oxygen saturation on the ear and no clinical, radiological or electrocardiographic signs of cardiac or pulmonary anomaly.

Discussion

Control of supplemental oxygen by measurement of arterial oxygen saturation depends on the ability of the ear oximeter to detect deviations both below and above the normal saturation level.

Below normal, changes in saturation are quite large in relation to changes in arterial oxygen tension, as the steep slope of the oxygen hæmoglobin dissociation curve in this area indicates. There is therefore no difficulty in detecting arterial desaturation oximetrically.

Above normal, the changes in saturation are small in relation to tension changes, as the oxygen hæmoglobin dissociation curve is almost flat in this area. It is this problem which requires further discussion in relation to the validity of the method of oximetric control.

Fowler and Comroe[14] have analyzed oxygen tensions and corresponding oximeter saturations obtained breathing air, 40% oxygen and 99.6% oxygen in normal persons. Their data and theoretical reasoning suggested that blood hæmoglobin was approximately 96-98% saturated at 100 mm. Hg oxygen tension with the subject breathing air. Following a period of 40% oxygen inhalation a mean increase in oximeter readings of 2.43% was found. It was calculated that this corresponded to an alveolar oxygen tension of 240 mm. Hg. If 100% oxygen was then administered, a further average increase of 0.89% was registered. The corresponding alveolar oxygen tension was about 657 mm. Hg. Small but definite and measurable oximetric changes in arterial saturation occur therefore with very large changes in oxygen tensions.

The findings of Fowler and Comroe[14] and Douglas and Edholm[15] suggest that oximetric oxygen saturation while breathing room air is about 96%. The breathing of 35-40% oxygen increases arterial oxygen tension by about another 100 mm. Hg. According to Douglas and Edholm 35% oxygen increases arterial oxygen saturation by about 3.5% to 99.5%. Any further increase in inhaled oxygen concentration results in a negligible change in oximetric saturation, a large increase in arterial oxygen tension and a relatively small increase in dissolved oxygen. It is interesting that 35% oxygen (arterial oxygen tension about 200 mm. Hg) appears, from clinical observation, to be the level above which retrolental fibroplasia is increasingly encountered in susceptible infants.

These considerations indicate that if an infant's blood can be shown to be 95-98% saturated oximetrically, the arterial oxygen tension is unlikely to be at dangerous levels. The relative accuracy of the oximetric saturation can be checked in an infant showing a normal saturation in air by

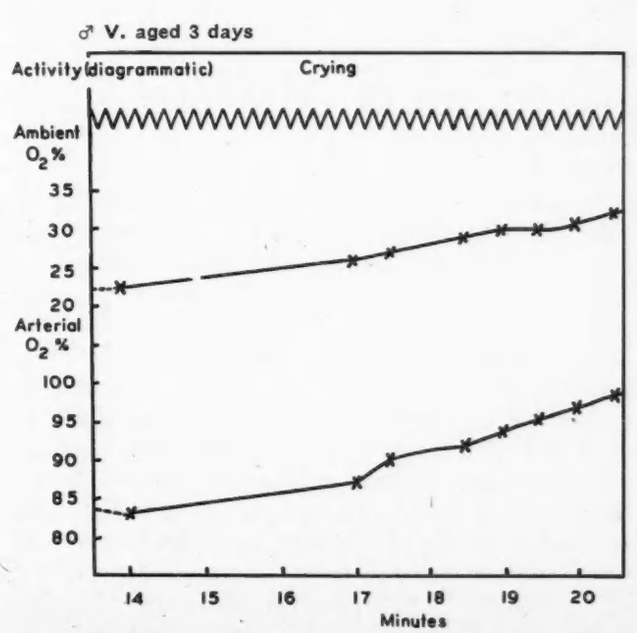

Fig. 4.—Birth weight 5 lb. ½ oz. Restoration of normal SaO_2 with 30% O_2.

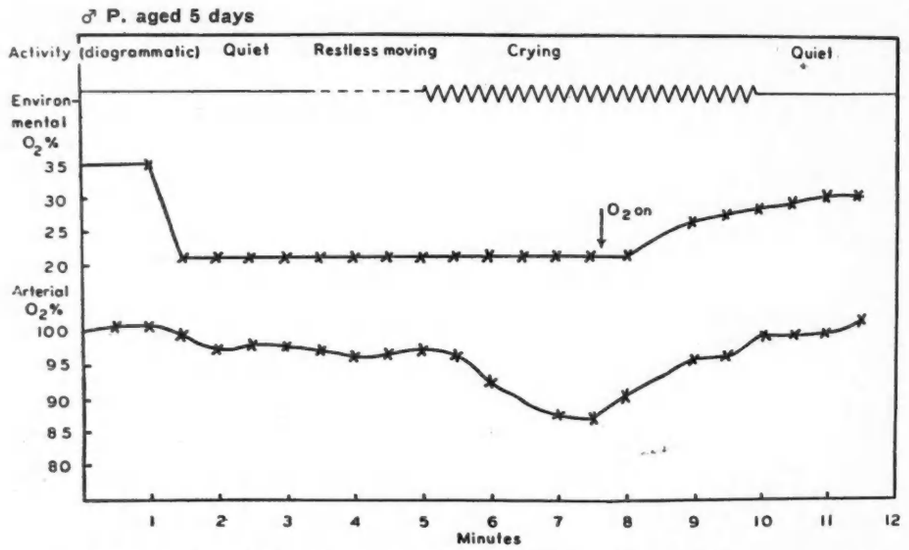

Fig. 5.—Birth weight 6 lb. 1 oz. This record shows a fall in SaO_2 on crying which is abolished by 30% supplemental oxygen.

giving 100% oxygen by mask to breathe for a short period. An increase in arterial oxygen saturation of the order of 3% would indicate normal saturation/tension relationships at the previous level.

It therefore follows that if inspired oxygen is limited to the minimum concentration which will produce approximately 96% arterial saturation measured by ear oximeter, the partial pressure of oxygen in arterial blood will remain close to the safe 100 mm. Hg level. Thus, by controlling inspired oxygen concentration and measuring at intervals arterial oxygen saturation the dangers of both hypoxia and hyperoxia will be avoided and a practical solution to the problem of control afforded (see Figs. 1 to 5).

It has been assumed in the foregoing discussion that there is no significant difference between the oxygen-hæmoglobin dissociation curves for fetal and adult bloods at oxygen tensions over 100 mm. Hg.

The number of cases in this series is too small for any firm conclusions to be drawn, but some insight has been gained into the sort of information to be obtained by oximetry in the newborn.

It is already well established[14] that the clinical assessment of hypoxia in adults is fallacious. Our observations have shown that about half of our infants receiving oxygen on clinical grounds did not in fact require it, if an arterial oxygen saturation of 96% in air is accepted as normal. It has however been the policy in this hospital to use oxygen in a concentration not exceeding 35% in cases showing dyspnœa and/or doubtful or episodic cyanosis, as an insurance against hypoxia. It has been felt that, provided the oxygen concentration is controlled strictly, there is little danger of retrolental fibroplasia even in small prematures. There has in fact been no known case of retrolental fibroplasia while this policy has been in force. With the advent of closer control by oximetry it may well be that oxygen can be dispensed with in these clinically borderline cases. Oxygen should continue to be available for the treatment of blue spells.

Of the remaining half in the series most required oxygen for five days or less.

There has been an increasing tendency to restrict oxygen to 35% without regard to individual requirements. The fact that one-third of our cases required more than 35% oxygen to achieve a normal saturation initially shows that this policy has its dangers. Serial daily observations on these cases indicated that, if recovery ensues, there is a progressive diminution in the percentage requirement for supplemental oxygen over four or five days (Fig. 7). Thus there is a case for the individual control of supplemental oxygen rather than the application of a blanket rule of percentage oxygen concentration. No concentration of oxygen, however high, is likely to result in retrolental fibroplasia to an infant weighing less than 1800 grams if central cyanosis (not peripheral cyanosis) persists while in that concentration. Persisting central cyanosis under these circumstances indicates that there is a block in the absorption of oxygen which cannot be surmounted by supplementing, or a central right to left blood shunt.

The demonstration of a central right to left shunt through a persisting ductus arteriosus in one case shows that arterial oxygen desaturation

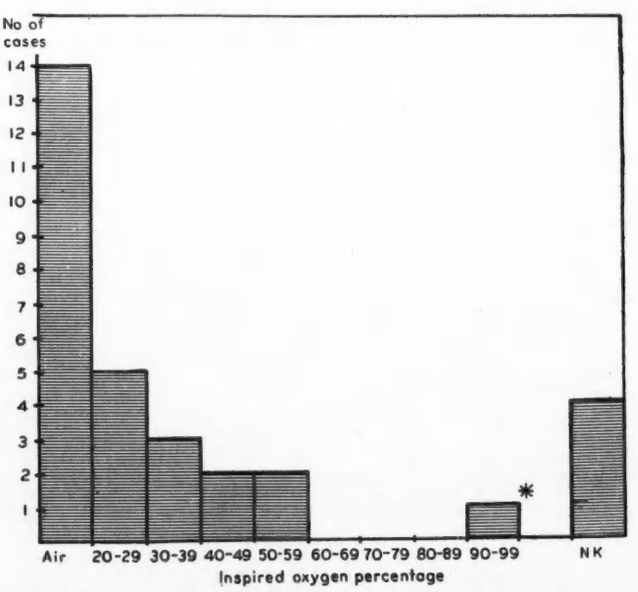

Fig. 6.—The distribution of 31 cases according to minimum inspired oxygen levels necessary for normal saturation. NK = Not known.
*Normal arterial saturation could not be obtained in this case even with pure oxygen.

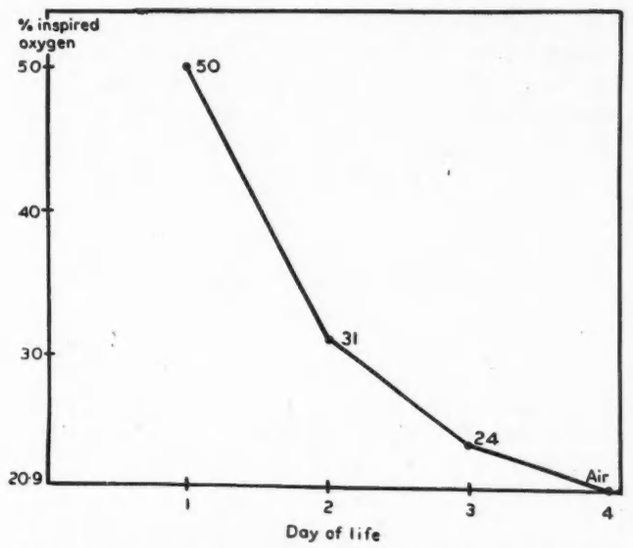

Fig. 7.—Case Br. This graph illustrates the daily reduction in minimum supplemental oxygen required for normal arterial oxygen saturation.

may not always be entirely respiratory in origin. Recent work[17] suggests that hypoxia may be accompanied by a raised pulmonary artery pressure in the newborn which would favour a right to left flow through fetal passages. There is therefore an intimate relation between pulmonary and hæmodynamic factors in the causation of arterial desaturation which requires further investigation.

Infants over 5 lb. (2270 grams) in birth weight are most unlikely to get retrolental fibroplasia under any conditions of partial pressure of arterial oxygen or ambient oxygen concentration. However, recent work[18–20] indicates that excessive oxygen may be a factor in the formation of hyaline membranes in the infant lung.

Our results indicate that oximetry can be used to control supplemental oxygen administration at the minimum level necessary to secure physiological oxygenation of arterial blood. Hyperoxia can be avoided in those weight groups susceptible to retrolental fibroplasia, and hypoxia due to ill-advised adherence to a rigid rule of thumb limitation of supplemental oxygen can also be eliminated.

It was noted incidentally that a normal arterial oxygen saturation could exist even in the presence of severe dyspnœa, and it was felt that dyspnœa alone was not a reliable indication for supplemental oxygen.

SUMMARY

This paper reports the results of an investigation into the use of the diamagnetic oxygen analyser and the Wood spectrophotometric ear oximeter in the assessment of arterial oxygen saturation in neonates and its relation to supplemental oxygen administration.

Almost half of the 31 infants probably received oxygen unnecessarily though not harmfully. Of those who required oxygen about one-third needed a percentage greater than 35 initially. The required level for normal arterial oxygen saturation dropped progressively over about five days to the atmospheric level (20.9%) in most cases.

Our thanks are due to the many members of the staff of the Hospital for Sick Children who kindly allowed us to investigate their patients, and to Mrs. B. Anderson for able technical assistance.

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RÉSUMÉ

Dans l'oxygénothérapie du nouveau-né, le pédiatre doit éviter le Charybde de l'hypoxie sans toutefois sombrer dans le Scylla de la fibroplasie rétrolentaire. Les auteurs de cet article ont cherché à vérifier les résultats produits par l'administration supplémentaire d'oxygène telle que dictée par les données cliniques. La saturation du sang artériel en oxygène fut déterminée chez 31 nourrissons en incubateur à l'aïde de l'oxymètre photoélectrique de Wood apposé au lobe de l'oreille, et l'analyseur d'oxygène diamagnétique. Les résultats ont montré que sans détriment à leur santé, près de la moitié du groupe de ces enfants reçut de l'oxygène sans raison suffisante. Par contre, environ un tiers exigea une concentration supérieure aux 35% qui forment la limite généralement acceptée dans l'administration d'oxygène au nouveau-né. De ce dernier groupe, la plupart des nourrissons qui survécurent n'eut besoin d'une telle concentration que pendant une période très brève; le besoin d'oxygène étant satisfait par la concentration atmosphérique normale après quatre ou cinq jours.

La difficulté dans l'administration de l'oxygène ne réside pas dans le dépistage de son déficit dans le sang, mais au contraire, dans la direction opposée. La courbe de dissociation de l'oxygène se termine à son extrémité supérieure par un plateau, de sorte que les quelques variations en oxyhémoglobine enregistrées par l'oxymètre ne se produisent qu'à la suite de fortes variations de concentration dans la tension d'oxygène. En somme, si le sang d'un enfant montre une saturation de 95 à 98% à l'oxymètre, la tension du sang artériel en oxygène ne risque pas d'être dangereusement basse, et il n'est pas nécessaire d'augmenter la concentration d'oxygène qui permet déjà ce degré de saturation. Les auteurs recommandent donc un usage plus étendu de l'oxymétrie dans l'oxygénothérapie afin d'en régler l'administration de plus près.

PREGNANCY AFTER PNEUMONECTOMY

It would appear from a small series of patients studied by Williams (*Brit. M. J.*, 2: 1087, 1957) that once a woman who has undergone pneumonectomy for tuberculosis has reached the stage of "apparent cure", childbearing presents no undue hazard provided her respiratory capacity is reasonably good. The follow-up so far has given no indication that the responsibilities of looking after a limited family are dangerous to her future health. Consultation between the obstetrician and the chest physician is of the greatest importance.

THE PHYSIOLOGICAL BASIS FOR SUPPLEMENTAL OXYGEN IN THE NEWBORN*

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INTRODUCTION

RECENT SURVEYS[1, 2] have clearly shown that one of the most important immediate causes of neonatal mortality is hypoxia, both prenatal and postnatal, chiefly in small premature infants. Prevention and treatment of antenatal hypoxia is an obstetric problem and beyond the scope of this paper. Postnatally hypoxia is associated with respiratory distress syndromes which include hyaline membrane disease, primary atelectasis, immaturity of the lung, aspiration of amniotic fluid, massive pulmonary hæmorrhage, neonatal pneumonia and spontaneous pneumothorax together with mixed syndromes of these conditions. It has been shown that 35-50% of total neonatal mortality is associated with these syndromes.[1, 2]

Towbin[3] has recently re-emphasized the importance of perinatal hypoxia in morbidity and mortality from cerebral damage. While hypoxia has been closely correlated clinically with such damage, there is at present no correlation of the objectively measured duration and extent of postnatal arterial oxygen desaturation with cerebral damage as shown in the various types of cerebral palsy.

Supplemental oxygen is the obvious essential treatment of hypoxia, but administration needs to be controlled by measurement of blood oxygen to ensure adequate relief. Small premature infants pose an additional problem in that over-oxygenation may result in blindness due to retrolental fibroplasia (RLF).[4-12] This results from the susceptibility of the vessels in the incompletely vascularized retina to constriction and obliteration by hyperoxia with subsequent fibroblastic overgrowth on return to normal oxygen levels. This condition largely though not exclusively affects infants below 3½ lb. (1590 g.) birth weight, corresponding roughly to a gestational age of 30 weeks or less.

Control is therefore necessary to avoid the dangers both of hypoxia and hyperoxia. To control supplemental oxygen without measuring the level of blood oxygen is akin to controlling insulin administration without measuring the level of blood sugar. It can be done but it is less than satisfactory in the acute case.

In order to help the physician to deal adequately with this problem of control, an attempt is made in this paper to relate knowledge of respiratory physiology to newborn infants, especially in regard to oxygen absorption. A review is given of processes by which oxygen enters the blood in the lung and thence reaches the tissues from the arterial blood.

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The Normal Processes of Respiration

Respiration in regard to oxygenating function can be divided into two stages, the first comprising those processes by which oxygen is absorbed into the blood through the lungs and the second those in which oxygen is made available to the tissues by arterial blood.

First Stage of Respiration (Absorption in the Lungs)

The lung processes in the first stage can be divided into tidal ventilation, distribution of inspired gases to the alveoli (or alveolar ventilation); diffusion across the alveolo-capillary membrane, and circulation of blood through the alveolar capillaries (Fig. 1).

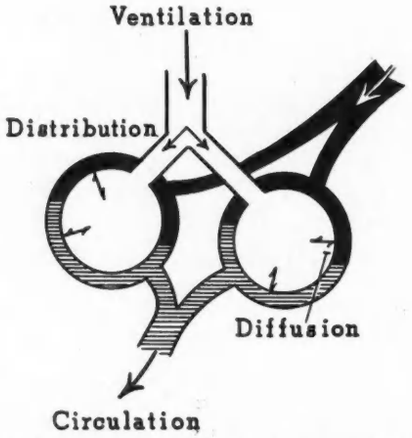

Fig. 1.—After Comroe, J. H., Jr. *et al.* in *The Lung*, Year Book Publishers Inc., Chicago (1955). The four processes concerned in the passage of oxygen from the atmosphere into the pulmonary blood.

In the normal individual, blood at the end of a pulmonary capillary will have reached equilibrium in regard to partial pressure of oxygen (PO_2)* with the gas in the alveolus at approximately 104 mm. Hg. Minor unevenness of distribution of inspired air will result in some alveoli being hypoventilated or unventilated. This, in effect, raises the total pulmonary dead space. Blood circulating round such alveoli will be exposed to less than the normal 104 mm. Hg partial pressure of oxygen (PO_2), and when this poorly oxygenated blood mixes with the pulmonary outflow the mean partial pressure of oxygen (PO_2) will be lowered to 95 mm. Hg (equivalent to 97.1% arterial oxygen saturation—SaO_2). This amounts to an alveolar-arterial oxygen pressure gradient of 9 mm. Hg. These relationships are illustrated diagrammatically in Fig. 2.

In respiratory distress in the newborn, recent work suggests that there is an increase in the physio-

*The physiological symbols used throughout this paper are those suggested by a group of respiratory physiologists meeting under the chairmanship of Pappenheimer and published in *Fed. Proc.*, 9: 602, 1950.
PaO_2 = partial pressure of oxygen in arterial blood. PO_2 = partial pressure of oxygen. PAO_2 = partial pressure of oxygen in the alveolus. SaO_2 = arterial oxygen saturation. DO_2 = oxygen diffusing capacity.

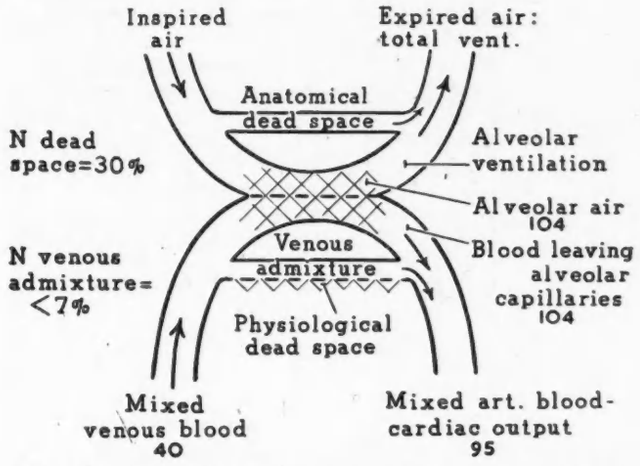

Fig. 2.—Illustrating blood/gas relationships. The figures refer to PO_2 in mm. Hg (modified from Riley, R. L. and Cournand, A., *J. Appl. Physiol.*, 1: 825, 1949). This figure is discussed in the text.

logical dead space up to twofold.[13] This may be compensated by an increase in minute volume due to tachypnœa, the tidal volume varying little. In this case, alveolar ventilation (V_A) remains approximately normal and the normal alveolo-raised alveolar-arterial oxygen gradient in proportion to the severity of the pathological changes in the lung. The extent by which diffusion difficulty and the exercise of respiratory effort could raise the alveolar-arterial oxygen pressure gradient can be appreciated by reference to the theoretically derived saturation-tension curves in Fig. 3 which are displaced to the right of the normal curve in proportion to the degree of intrapulmonary shunt and diffusion difficulty.[14]

Second Stage of Respiration (Transfer of Oxygen to the Tissues from Arterial Blood)

This depends on the availability of oxygen in arterial blood and an adequate peripheral circulation. Availability is determined by the shape of the oxygen hæmoglobin dissociation curve, where degree of saturation is related to partial pressure of oxygen (PO_2) (Fig. 4).

The normal partial pressure of oxygen in arterial blood (PaO_2) is 95 mm. Hg. If on the one hand a rise in the percentage of inhaled oxygen results in a rise in partial pressure of oxygen in arterial blood (PaO_2), the premature infant will—at a

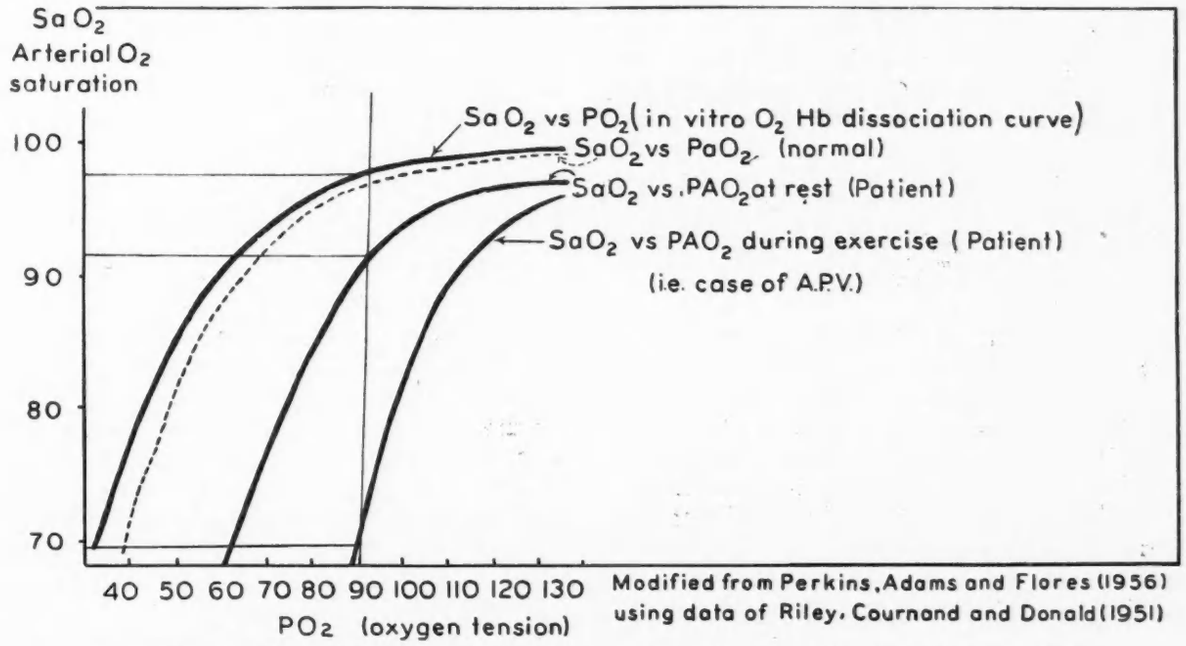

Fig. 3.—Theoretical saturation/tension curves to illustrate the separate components making up the total alveolar-arterial gradient for PO_2. The distance on the abscissa between a given point on a curve and the iso-saturation point on the *in vitro* O_2 Hb-dissociation represents the alveolar-arterial gradient. It will be noted that exercise in a patient with a limited DO_2 displaces the curve to the right in such a way that, at a PO_2 of 88 mm. Hg, the SaO_2 is only 69% compared with the resting SaO_2 of 92% at the same PO_2 of 88 mm. After Perkins *et al.*, 1956.[14] (A.P.V. = abnormal pulmonary ventilation.)

capillary pressure gradient is maintained. If, through exhaustion or obstruction to air flow, minute volume cannot be increased, blood gas homœostasis will fail and an increased alveolo-arterial pressure gradient results.

This gradient may be further raised by concomitant diffusion difficulty. This difficulty is aggravated by the increased diffusion necessary to supply more oxygen demanded by the increased respiratory work of dsypnœa. The net result is a certain level for a certain time—run the risk of developing retrolental fibroplasia (RLF). Recent work[12, 15] suggests that 35-40% oxygen for two to seven days is critical. Douglas and Edholm[16] have shown in adults that an arterial oxygen saturation of 99.5% corresponds to an alveolar partial pressure of oxygen of 212.9 ± 7.7 mm. Hg. Assuming an alveolar arterial pressure gradient of 10 mm. Hg, this would result in an arterial oxygen tension of approximately 200 mm. Hg. Reference to Fig. 4

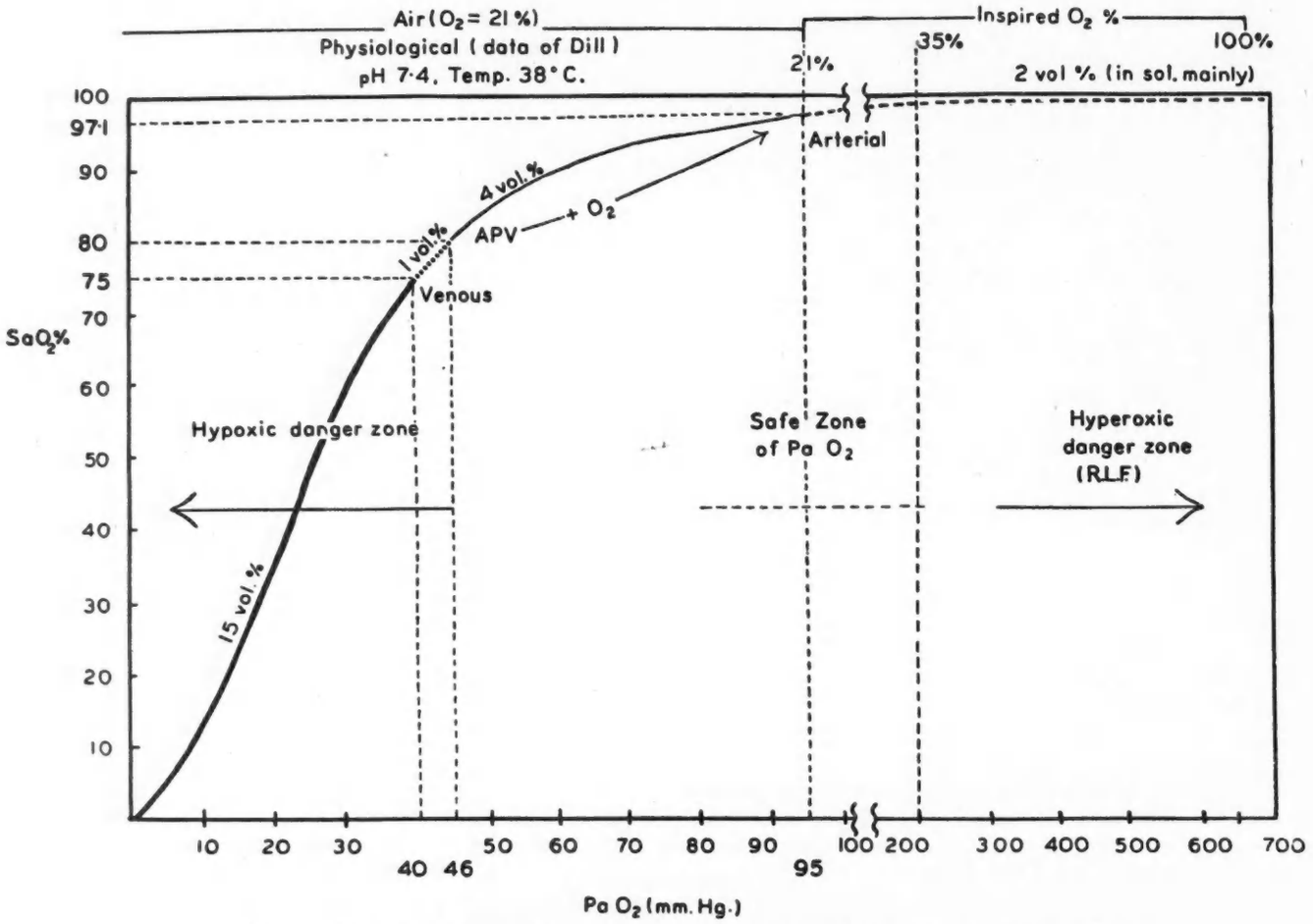

Fig. 4.—The oxygen hæmoglobin dissociation curve extended to cover the range of PaO_2 encountered with supplemental oxygen up to 100% at a pressure of one atmosphere. The volumes % of oxygen available between different arterial partial pressures of oxygen are indicated on the curve. The effect of supplemental oxygen in restoring a case of abnormal pulmonary ventilation to the physiological safe zone of PaO_2 is also indicated. Note that the scale of the abscissa changes above 100 mm. Hg. This diagram is further discussed in the text. (A.P.V. = abnormal pulmonary ventilation.)

will show that 40% of inspired oxygen, in the absence of a defect in absorption, will result in a partial pressure of oxygen in arterial blood (PaO_2) of about 240 mm. Hg or about 2½ times the normal figure. It is this high partial pressure of oxygen in arterial blood (PaO_2) which is responsible for initiating the vasoconstrictive and vaso-obliterative changes of retrolental fibroplasia (RLF). A partial pressure of oxygen in arterial blood (PaO_2) of around 240 mm. Hg and above is therefore dangerous.

On the other hand, in a hypothetical case of a newborn infant with an oxygen absorption defect breathing air, the arterial oxygen saturation (SaO_2) might be reduced relatively slightly to, say, 80%. At this arterial oxygen saturation (SaO_2) the partial pressure of oxygen in arterial blood (PaO_2) is about half of normal and is almost at the "venous" point on the dissociation curve.

Reference to Fig. 4 shows that there is a pressure head of oxygen of only 6 mm. Hg available over the normal "venous" point on the dissociation curve corresponding to the availability of only 1 vol. % oxygen. Compare this with a pressure head of 55 mm. Hg and 5 vol. % oxygen available at a normal 97.1% arterial oxygen saturation (SaO_2). There is, therefore, a danger of hypoxic tissue damage, though other factors such as tissue tolerance to hypoxia, increased oxygen extraction by the tissue due to a low tissue partial pressure of oxygen (PO_2), volume of local blood flow and oxygen carrying capacity of the blood[17] affect the final outcome. Of course many cases of respiratory distress may have an arterial oxygen saturation (SaO_2) well below 80% with a consequently greater danger of tissue hypoxia.

The aim of supplemental oxygen therapy in respiratory distress should therefore be the restoration of partial pressure of arterial oxygen (PaO_2) to the "safe" area around 95 mm. Hg, corresponding to an arterial oxygen saturation (SaO_2) around 95-97%. If oxygen is given in a concentration just sufficient to achieve this, the dangers of both hypoxia and hyperoxia (RLF) will be avoided no matter what the percentage of inspired oxygen may be.

The problem is to recognize in the patient the danger areas of partial pressure of oxygen in arterial blood (PaO_2) to both sides of physiological norm. There is as yet no satisfactory direct method of estimating partial pressure of oxygen in arterial

blood (PaO_2) *in vivo*, though the oxygen polarograph is promising.[18]

At present most clinicians rely on a combination of physical signs and symptoms, of which the most important is probably cyanosis, to indicate that the infant may be in the hypoxic danger zone. The hyperoxic danger zone is avoided empirically by limiting the duration of therapy to less than seven days and the percentage of oxygen to below 40, on the basis of the previously observed fall in incidence of retrolental fibroplasia (RLF) resulting.[19] This policy has been shown to be without adverse effect on neonatal survival or growth and development[19, 20] and is largely effective in eliminating retrolental fibroplasia (RLF). There is probably little danger of transgressing the upper hyperoxic danger zone with adequate control of oxygen percentage around 35%* but this may not be true of the lower hypoxic zone for two reasons.

Firstly, it has been shown that the ability to recognize cyanosis clinically varies from person to person and even in the same person at different times.[22] In addition to this personal factor there are the well-known pitfalls in regard to total hæmoglobin content and sluggish peripheral circulation, especially pertinent in the newborn. Thus the most generally accepted clinical indication for supplemental oxygen is fallible. Cyanosis, moreover, even if recognized, can only be very grossly correlated visually with arterial oxygen saturation (SaO_2).

Secondly, some cases with severe defect in the absorption of oxygen in the lungs may require a percentage of oxygen considerably above the usually safe upper limit of 35-40% to achieve a partial pressure of oxygen (PaO_2) within the safe zone.[23] Thus, some cases, even with 35% supplemental oxygen, may remain in the hypoxic danger zone.

The numbers in this latter category are unknown, but it is possible that an occasional case may require a very high percentage of oxygen if not pure oxygen to achieve a partial pressure of oxygen in arterial blood (PaO_2) within the safe zone. From what has been said above there is theoretically no danger of hyperoxic retinal vascular changes provided the oxygen is limited to the minimum necessary by oximetric control of arterial oxygen saturation (SaO_2).† All such problem cases should probably have the benefit of special control techniques, which would involve frequent monitoring of the infant's inhaled oxygen concentration and arterial oxygen level.

It is possible that some of these infants who remain cyanosed neonatally in spite of high inspired oxygen concentrations may have a central right-to-left shunt through patent fetal passages (ductus arteriosus, foramen ovale) because of the effect of hypoxia in raising further the already high pulmonary artery pressures of the newborn.[26] It follows from what has been said earlier that the partial pressure of oxygen in arterial blood in such cases will remain low and there is therefore no danger of retrolental fibroplasia.

*It is still not uncommon to hear oxygen prescribed in terms of flow in l./min. rather than in precisely controlled percentage. This is an extremely dangerous practice in view of the high concentration attainable in modern incubators with low rates of flow.[21]

†Respiratory epithelial damage may occur in the 70 to 100% range if such atmospheres are maintained for longer than four hours in the normal adult.[24] If there is already pulmonary damage, the resulting œdema appears to protect the respiratory epithelium from further hyperoxic damage, and high concentrations of oxygen can probably safely be given.[25]

SUMMARY AND CONCLUSIONS

Supplemental oxygen is of prime importance in reducing the neonatal mortality and morbidity due to hypoxia, but a surfeit for the premature infant may entail blindness due to retrolental fibroplasia. The physician's problem is to avoid this surfeit while supplying enough oxygen to overcome the barrier to absorption posed by the immature or diseased lung.

A review is given of the processes by which oxygen enters the blood in the lung and thence reaches the tissues from the arterial blood. This suggests therapeutic principles and control techniques to guide the physician where the closest clinical observation may be fallacious.

If any improvement is to be made in morbidity and mortality from neonatal hypoxia and hyperoxia, it will be necessary to recognize by objective measurement the special problems posed by the disordered respiratory mechanism.

Since oxygenation of the tissues by arterial blood is one of the fundamental functions of repiration, it is suggested that objective measurement of the degree of oxygenation of arterial blood is one of the essential adjuncts to the treatment of cases in this special group with supplemental oxygen.

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RÉSUMÉ

Un apport supplémentaire d'oxygène est d'importance primordiale dans l'abaissement de la mortalité et de la morbidité causées par l'hypoxémie du nouveau-né, mais un excédent peut causer la cécité chez les prématurés en déclanchant la fibroplasie rétrolentaire. Le problème se pose dans la détermination de la quantité d'oxygène qui doit être suffisante pour surmonter l'obstacle que présente le poumon pathologique ou prématuré et qui doit cependant rester en deça de la concentration nocive pour l'œil. L'auteur offre un rappel des processus par lesquels l'oxygène pénètre dans la circulation par les poumons et de là atteint les tissus par l'entremise du sang artériel. D'après ces données, il suggère certains principes thérapeutiques ainsi que des moyens de contrôle technique qui peuvent aider le médecin dans la conduite du traitement là où les observations cliniques même les plus perspicaces pourraient être erronées. La nécessité de reconnaître par des moyens objectifs les problèmes spécialisés que représentent les troubles du mécanisme respiratoire est à la base de tout progrès dans le domaine de l'administration de l'oxygène. Puisque l'oxygénation des tissus par l'hématose constitue une des fonctions fondamentales de la respiration, l'auteur suggère que la détermination objective du taux d'oxygène dans le sang artériel forme le pivot de l'oxygénothérapie.

A SURVEY OF BURNS AT THE VANCOUVER GENERAL HOSPITAL FROM 1946 TO 1955

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VARIOUS EXCELLENT PROGRAMS for management of burns have been well described and documented over the last ten years.[2-3] It is our purpose to indicate the results that follow the many different interpretations and applications of these in a large open hospital.

The burns have been grouped as superficial or deep, indicating partial-thickness or full-thickness skin destruction respectively; mixed types of burns have been placed in the latter group. During the period from 1946-1955, 780 patients with burns (528 superficial and 252 deep) were admitted at periods varying from a few minutes to several months after the injury. Early in the series it was common to receive a patient burned three weeks or more previously; this was usually due to failure to recognize the depth of the burn until the necrotic skin separated. Now there is a general appreciation of the characteristics of a deep burn; the patient usually arrives within the first few days and it is rare to get an old untreated burn.

Fig. 1 illustrates a progressive decline in the admission of patients with superficial burns. This is attributed to wider knowledge of the recognition of the degrees of burns by the profession, and to the onset of the British Columbia Hospital Insurance Scheme in 1947, with an associated rise in population which resulted in a scarcity of hospital beds making admission of patients with this degree of burn difficult. Since only extensive superficial burns require hospital care, this decline has saved money and no one has suffered unduly. Although the incidence of burn admissions has not increased, there has been a decrease in the ratio of superficial/deep from 4:1 to 2:1 for the same reasons. Additionally, skin grafting on the smaller burns is now being more widely performed in hospitals throughout the province, whereas formerly such cases were transferred. Now it is usually the extensive burns that are sent in.

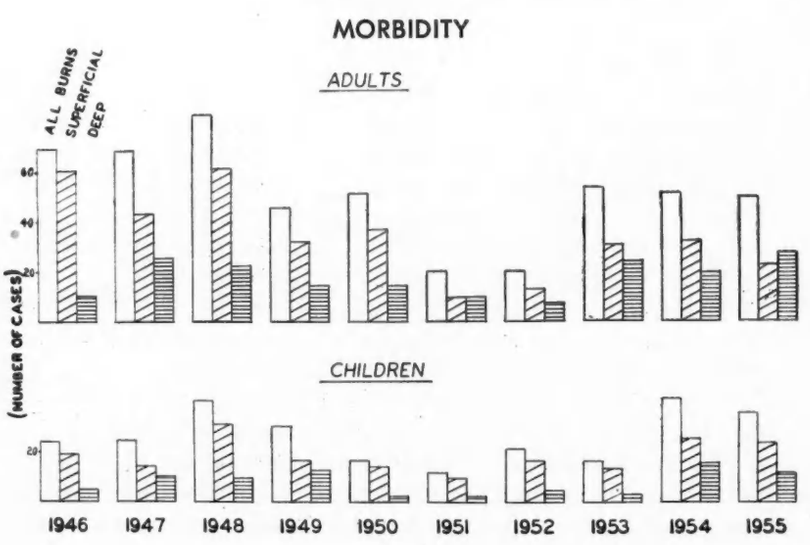

Fig. 1

The causes were as follows: flame—314, scalds—237, chemical—36, electrical—27, direct heat—117, not stated—49. As expected, flames and scalds were the most common, the former more frequently causing a deep burn and the latter a superficial burn. There is a greater incidence of scalds in children; these were largely due to home accidents. Flame burns on this coast frequently resulted from

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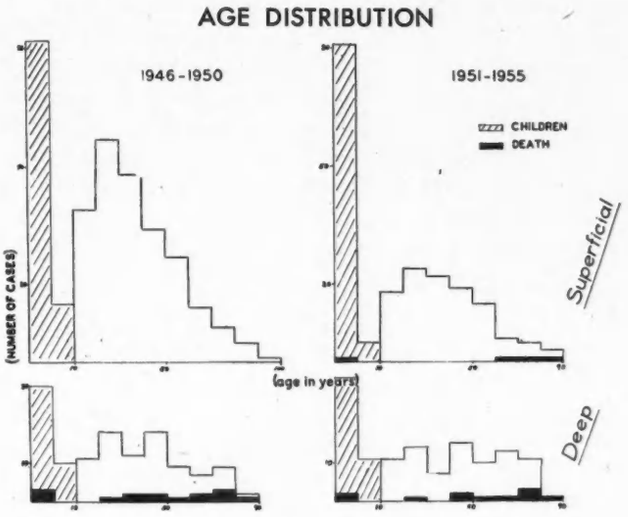

Fig. 2

the various combustible agents used in heating and lighting, and in the operation of boats; this would indicate that some safer agents are desirable for these purposes.

Fig. 2 shows that the preponderance of admissions was of children under 10 years of age, comprising one-third of the total and one-third of the deep burns. This again illustrates the frequency of home accidents; a reduction can scarcely be expected, because of the human element involved. The mortality rate illustrated in Fig. 4 amounts to 2.6% for children and 5% for adults, with an all-inclusive rate of 4.2%. This great difference was due to adults receiving more extensive burns—usually from flames, which caused 80% of the deaths. As expected, there were also more deaths in the age groups under five years and over 60 years—seven and twelve respectively. No survivals occurred where deep burns involved 45% or more of the body surface, and the mortality rate increased when the burn exceeded 25% (Fig. 3).

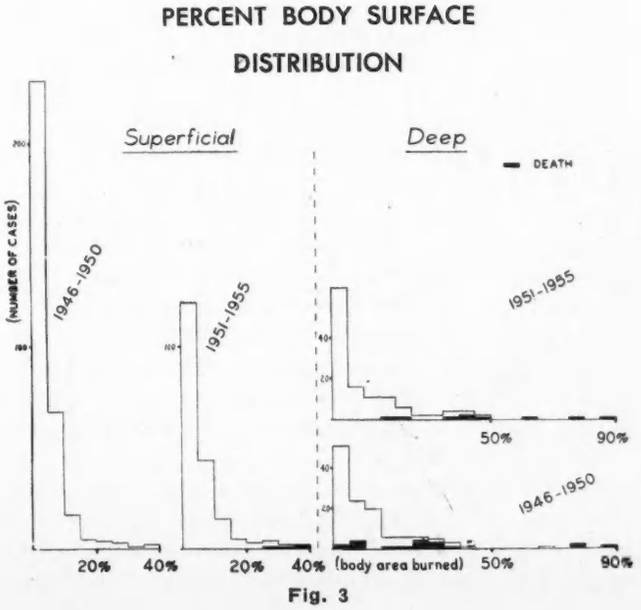

Fig. 3

This would confirm Moyer's statement: "There has been little change in the death rate in burns over 25% since 1905."[4]

Because of scanty information on many of the records it was difficult to determine a single immediate cause of death (Table I). In the first two days after the burn, shock was the most common cause; however, pulmonary œdema was also often associated. Pulmonary œdema and bronchopneumonia predominated separately and together from the second to the 11th day. The most frequent cause from the fifth to the 15th day was an acute tubular degeneration of the kidneys as indicated by anuria or oliguria, but it was occasionally associated with a degree of hepatitis or of pulmonary involvement. In these cases it was difficult to separate

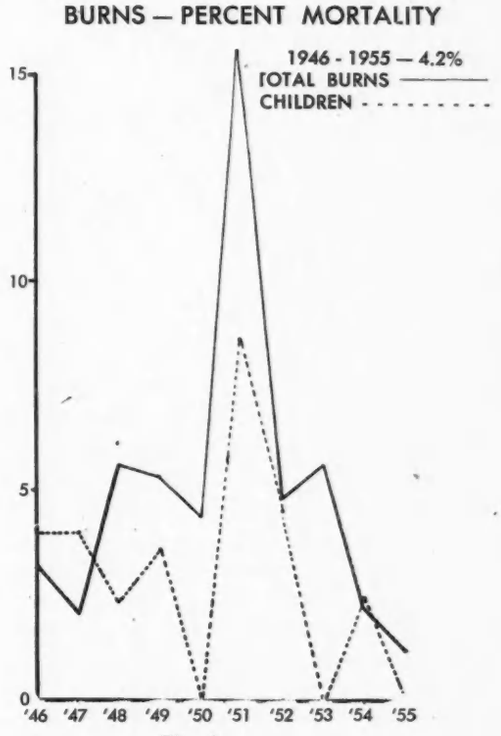

Fig. 4

the immediate cause where the urinary output was reduced but where there were no changes in the blood chemistry to indicate a uræmia. The only single proven death from hepatitis was in a burn not exceeding 10% of the body surface in a 10-month-old child who had been given 200 c.c. of blood and 800 c.c. of plasma on admission. He was skin-grafted and discharged as healed on the 59th day, only to be readmitted and die on the 66th day. Review of the hospital records for the same period reveals serum jaundice in only two other patients given plasma for the treatment of burn shock; both of these recovered.

Two cases of septicæmia occurred and both patients died. This incidence is low in view of the findings of Liedberg, Rees and Artz:[4] "If the presence of septicæmia had not been recognized, 16 of the 35 deaths would have been classified as resulting from unknown causes. Perhaps these

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TABLE I.—BURN DEATHS, 1946—1955

SHOCK (*11*)			RESPIRATORY (*10*) *Pulmonary œdema (8)*			RENAL (*7*) *Acute tubular degeneration (6)*		
F2 28%	F2 90%	M4 30%	M1 50%	M1 40%	M40 7%	F33 30%	F49 85%	M53 45%
6 hours	½ hour	10 hours	1 day	8 hours	1 day	10 days	8 days	6 days
M56 80%	F69 45%	M70 40%	M43 65%	M47 30%	F49 80%	M65 35%	M78 40%	M78 25%
4 hours	2 days	2 hours	4 days	20 hours	8 days	5 days	6 days	15 days
M72 10%	M76 35%	M76 20%	M60 35%	M70 30%		F61 25%	*Acute bilateral pyelonephritis (1)*	
10 hours	5 hours	22 hours	5 days	1 day		107 days		
			Bronchopneumonia (2)			HEPATITIS (*1*)		
M84 40%	M88 35%		M43 18%	M45 45%		M1 10%	(Serum jaundice)	
8 hours	1 hour		2 days	11 days		66 days		
SEPTICÆMIA (2)			MISCELLANEOUS (*2*)			Total burns..... 780		
F29 81/41%	M79 30/1%	Positive Blood Culture	M52 7%	F1 1%	Convulsion–? Whooping cough	Total deaths..... 33		
45 days	44 days		5 days post-op.	1 day		% Mortality..... 4.2		

Top Line: Sex, age. *Middle Line:* Percent body surface burn. *Lower Line:* Interval between burn and death.

deaths would have been ascribed to toxæmia or to some equally obscure and ill-defined entity." Cultures of the burn surface and of the blood have not been carried out as frequently as they should; perhaps if this practice had been a routine, other cases of septicæmia would have been identified. One death on the 44th day occurred in a 79-year-old man who had a 30% body surface burn of which less than 1% was deep. He had been grafted and was almost healed at the time of the septicæmia, which was proven by blood cultures. The other death occurred on the 45th day in a patient with a deep burn involving 41% of the body surface, who had been grafted three times and whose burn was partially covered with skin. Septicæmia was evident both clinically and at autopsy, but no positive blood culture was obtained.

Generally, there were no deaths attributable to inadequate management of the shock phase, in spite of the fact that frequently no obvious program was being followed, and that the initiation of intravenous therapy was often delayed for several hours. The latter was common when the interns had not been given a routine to follow and impressed with the importance of immediate resuscitative measures. This is well illustrated in the case of one child admitted at midnight; a patch test for tuberculosis was performed before the intravenous drip was started. This child vomited at 8:00 a.m. and died one-half hour later. Death was probably inevitable, as the child had facial burns, but whether it died from pulmonary œdema or aspiration could not be stated definitely.

Early in the series there was a tendency to care for the burn surface before controlling shock, but now the latter is overcome before applying local therapy. Narcotics were generally used to control pain and restlessness, but now the latter is recognized as the more important problem and is managed by sedation. Accordingly, smaller amounts of narcotics are being used, thus reducing the hazard of depression in elderly patients.

PARENTERAL THERAPY

In the entire series many patients received parenteral therapy for shock that did not require it. Burns involving under 15% of the body surface in adults, and 10% in children, very rarely require administration of fluids by this method, particularly if superficial. It was not uncommon to find fluid given intravenously on admission and the patient discharged as healed in a few days. No harm was done by this, but it was unnecessary and uneconomical in expense and labour. From 1946 to 1950, the trend was to administer fluids in amounts calculated from the degree of hæmoconcentration as recommended by Harkins, or from the body surface area involved, using Berkow's charts. Rarely were the amounts controlled well, in comparison with the present-day standards of Cope[6] and Evans,[7] using the body surface area and body weight formula. The latter is now in general use here. Although quantities were often inadequate in this period, it could not be shown that any patient suffered from insufficient or excess fluids. In the same five-year period, concentrated plasma was used for the purpose of decreasing fluid loss into tissues from the intravascular compartments. The volume of fluid administered by this method is also not considered adequate now, but it seemed to serve the purpose during that period. The popu-

larity of plasma can be noted by the fact that 25,000 c.c. was given for shock in 1946, and in the same year only 4200 c.c. of whole blood was used. In 1955, this condition was reversed; plasma was used in two cases of burns to a total of 950 c.c. and blood was given to 11 patients with burns to a total of 14,950 c.c. Plasma is no longer available except for a reserve of virus-free stock maintained by the Red Cross Society for extreme emergencies. This group first provided serum albumin in 1955; now that it is more readily available it is in common use. During the last three years of the series, although dextran had been generally used elsewhere, it was administered here to only a few patients (total 8000 c.c.). This was due to the influence of the anæsthesia department which had some unfortunate experiences with this solution; as a result only polyvinylpyrrolidone (P.V.P.) was readily available, and so more widely used. No adverse effects were noted from this solution.

At present all patients with burns that exceed 25% of the body surface area are given blood to the extent of 50% of the plasma expander requirements, and the other 50% is made up with serum albumin. A more widespread appreciation of the red blood cell destruction initially and the early development of secondary anæmia has resulted in more frequent and earlier transfusions, and is probably a factor in successful skin grafting.

Laboratory Studies

With the exception of hæmoglobin, hæmatocrit and plasma protein estimations, which have been used in varying frequencies, only in the last few years have serious attempts been made to determine the blood changes. Determination of hæmoglobin level has been the laboratory procedure of most consistent practical value. Although low plasma protein levels have been noted, this estimation could not be shown to be of any real value in any single case. The potassium, chloride and bicarbonate content of the blood was rarely studied, but no one patient's clinical course seemed to suffer from these deficiencies. None of the deaths could be attributed to electrolyte disturbances directly. Acidosis was not noted. Rather generally in the last few years Moyer's solution has been given orally, as it should, since the electrolytes are better assimilated this way. Its effect on the eventual outcome is not possible to state in this series.

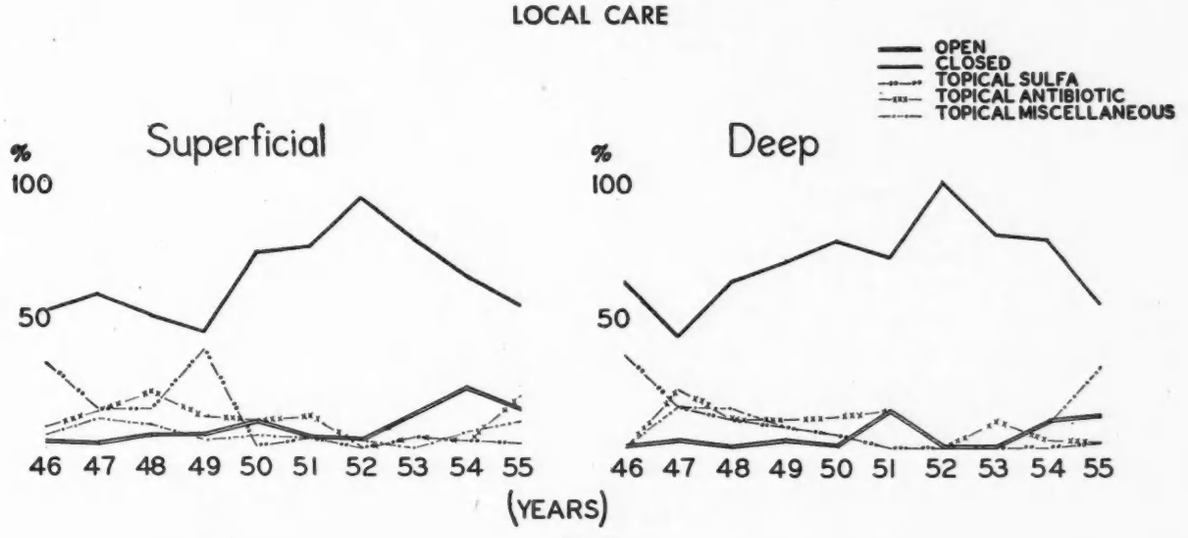

Fig. 5

More recently, fluid intake and output have been charted with some consistency. The use of an indwelling catheter has become common practice in severe burns and permits an accurate urinary output determination. This has greatly assisted in assessing the response of shock to therapy. The water tolerance test of Cope was used in two cases of severe burns where the output was reduced, but it did not help significantly. These patients were elderly and in pronounced shock. The hourly output did not increase and they died in the shock phase with a persistent oliguria.

Although prophylactic treatment against tetanus is commonly recommended, it was not given very frequently in this series. Perhaps it is only good fortune that some deaths did not occur from this cause.

Local Care

The local care of burns has generally been performed in the emergency department, and has consisted of simple cleansing with various antiseptics and application of an occlusive dressing. The latter has been too frequently inadequate in bulk to absorb satisfactorily; as a result, it would be wet by the next day. A few days later, when changed, the burn surface would be almost invariably infected from bacteria entering through the interstices. In the last year, a previously prepared dressing which is bulky, single and effectively

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absorbent, as described by Davis *et al.*,[8] has been made readily available; it is less prone to external contamination. The exposure method has been usually used for the face and ano-genital region, but during the last two years for other regions (Fig. 5) in a small number without any particular alteration of the result being effected. In the first five years less than one-half of the patients have had a topical agent applied. This was most frequently one of the sulfonamide preparations, and almost as commonly a penicillin powder or ointment. A wide variety of chemicals was also used. During the last five years the use of sulfonamides has almost completely been discontinued, but more recently the newer antibiotics have come into use to a minor degree. Since the larger number of cases have had nothing applied locally, they could be used as a control series. Without statistical proof because of so many variations, it can be stated that the application of topical agents has no special value. Neither method prevented deep burns from generally becoming superficially infected. There has been more effort during the last few years to use bacteriological control as a guide to use of a specific drug. It is now common practice to give an antibiotic parenterally or orally, and change it as indicated by the result of the culture taken at every dressing change.

GRAFTING

A significant improvement in the time from the burn injury to the application of the first skin graft is illustrated in Fig. 6, which shows a high of 36.9

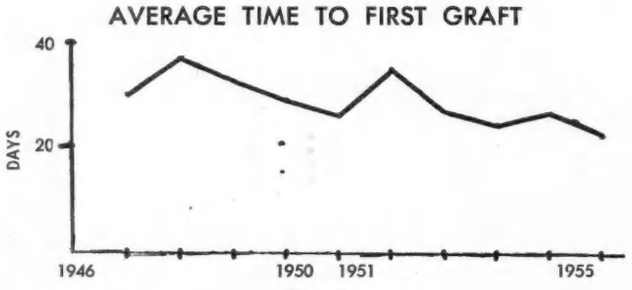

Fig. 6

days in 1947 and a low of 22.6 days in 1955. This trend has been noted by Farmer,[9] Robertson[3] and Woolhouse,[10] and has been attributed to earlier recognition and appreciation of full-thickness skin destruction by the attending surgeon. Another factor is the more rapid preparation of the burn surface for skin grafting. Early in the series this was done (Fig. 7) by the frequent changing of moist dressings from the time the deep burn was recognized, or less frequently by saline baths —both of which cause separation of necrotic tissue by the slow process of moist gangrene. More recently the burn area has been prepared for grafting by debridement under anæsthesia, using gauze to rub off the necrotic tissue, or by actual excision (Robertson[3] and Woolhouse[10]). Since the excision is carried into viable tissue, some of the latter must be sacrificed. It should never be practised on the face, which would result in loss of contour, or on the hands or feet where tendons or joint capsule may be exposed. This has been applied with greater frequency, but now the skin graft is not applied until two to three days after the excision. Formerly the graft was applied immediately, but this frequently resulted in only a partial take as the graft would be lifted off the recipient area by serum or blood. The delay overcomes this by allowing formation of flat, red granulation tissue

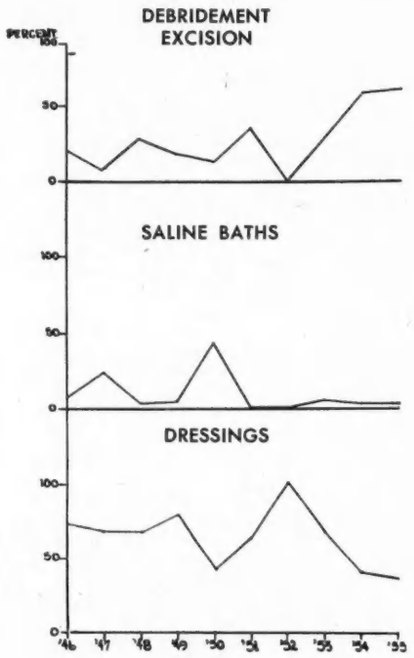

Fig. 7

upon which a skin graft readily survives. Before starting this study it was considered that the above practices should reveal a general trend towards reduction in the average number of skin-grafting operations per patient—the high was 2.6 and the low was 1.2—but this was not found. This should become more apparent in the next five years. It was also believed that the size of the average graft per operation would be larger—this varied from a high of 65.3 square inches to a low of 21.9 square inches—but such was not the case. The size of the graft was rarely recorded, and an attempt made to estimate this was really inaccurate because of the limited description on the records. With these policies, however, personal experience has indicated that the number of grafting procedures is reduced and that larger areas are more successfully covered with skin in a single operation. Its effectiveness is readily shown in Fig. 8, which illustrates a gradual decrease in the days to healing of deep burns—defined as the time from receiving the burn to discharge healed from hospital—from a high of 73.3 days in 1946 to a low of 46.4 days in 1955. The reduction in morbidity is quite significant, and a considerable financial saving has been effected in these days of high hospital costs. These times

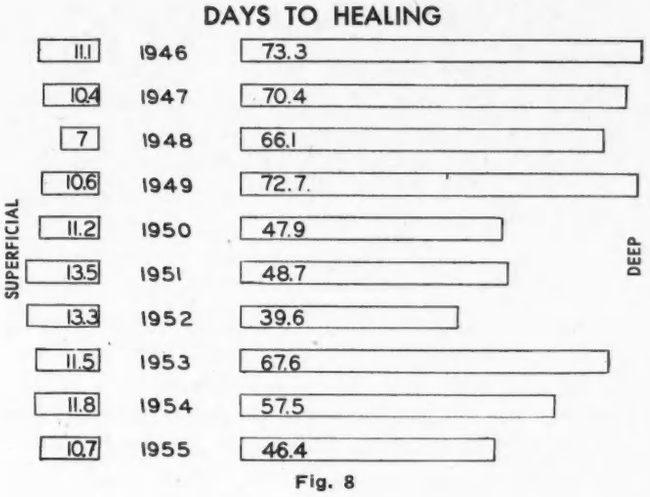

Fig. 8

can be reduced further when the value of grafting in the optimum third week after the burn is more widely appreciated, and to the minimum when a clinical or laboratory test becomes available to allow definite recognition of deep burns on the first day, along with some method for producing immediate separation of necrotic skin.

CONCLUSIONS

A review of 780 burns over a 10-year period at the Vancouver General Hospital reveals generally adequate care, although treatment has been by many different surgeons with a multitude of methods.

Tendencies to unnecessary and inadequate intravenous therapy in the treatment of shock have been noted, but these excesses have been corrected by the more widespread knowledge and use of the body surface area/body weight formula of Evans.

It is not possible to show that the application of topical agents affected the course of a burn materially.

A rather low incidence of septicæmia was found, but this might be attributed to the infrequent use of blood cultures.

Better understanding of the method of preparing the burn area for skin grafting has resulted in earlier grafting with resultant reduction in morbidity and hospital stay.

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RÉSUMÉ

Dans la période s'étendant de 1946 à 1955, 780 brûlés furent admis à l'hôpital général de Vancouver. Les auteurs de cet article ont entrepris de faire une revue générale de tous ces cas. En dépit de la diversité dans la manière d'aborder et de diriger le traitement et malgré le nombre de chirurgiens entre qui ces cas furent répartis, les résultats se montrèrent en général assez satisfaisants. L'usage des solutés intraveineux dans la réanimation des malades en état de choc s'améliora avec une meilleure connaissance du sujet et avec l'application de la formule d'Evans basée sur la surface cutanée par rapport au poids. Les différentes médications topiques ne semblent pas avoir influencé l'évolution des blessures en aucune manière. On ne rapporta qu'un nombre assez restreint de septicémies; mais encore faut-il ajouter que les hémocultures ne furent pas nombreuses. Une meilleure connaissance de la manière de préparer les surfaces brûlées en vue des greffes, a conduit au greffage plus précoce et a contribué à la diminution de la morbidité ainsi que de la longueur du séjour à l'hôpital.

THE POTENTIATION OF OBSTETRIC ANALGESIA
A PRELIMINARY REPORT ON MEPAZINE (PACATAL)

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INTRODUCTION

THE METHODS of providing analgesia in the first and second stages of labour are many, and the combinations of agents used are almost as varied as the patients receiving them. This must necessarily be so because of the individuality of each labour in each patient, but the differences are in part due to the differing aims of the supervisors. Some argue that total amnesia is necessary and desirable;[1] others believe drugs to be unnecessary in normal labour.[2]

Most obstetric units in this country adopt a middle course, using non-volatile hypnotics and analgesics during the first three-quarters of the first stage, and volatile agents thereafter,[3] which provide adequate analgesia for the majority of patients.

POTENTIATION OF OBSTETRIC ANALGESIA

All supervisors of labour make use of some form of calming agent to improve the effectiveness of the analgesic agents used, whether it be reassurance and explanation, autosuggestion, hypnotism or drug-induced euphoria. The most effective form is the constant presence of a strong personality with the patient throughout her labour, but this is rarely practicable in most busy units, and patients

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may be left alone for variable periods in which they readily become anxious and demoralized. In these circumstances the effectiveness of analgesics is much reduced, and larger doses may be required to afford relief. Some patients have immature personalities and may be inaccessible to reassurance, providing difficult management problems, often involving heavy sedation. These increased dosages inevitably increase the risk of depression of fetal respiration.[4]

If the emotional tension and fear associated with labour in many patients—especially in primigravidæ—can be removed by these calming agents, the need for analgesic agents is reduced and the effectiveness of a given dose increased.

PHENOTHIAZINE DERIVATIVES

A number of drugs recently introduced into medicine produce tranquillity without analgesia or hypnosis, and have been called "ataractics" or "tranquillizers". Some of these are phenothiazine derivatives which, in addition to the production of a state of calm apathy, also potentiate hypnotics and analgesics and have anti-emetic properties. Peripherally, adrenergic blockade and reduction of smooth muscle tone may cause vasodilation and postural hypotension. Parasympathetic activity is reduced, with atropine-like effects, and antihistaminic and local anæsthetic activity may be present. Respiration is usually stimulated.

All phenothiazine derivatives share the same effects, but the prominent effects differ markedly with each drug and have found application in psychiatry, anæsthesia and obstetrics, and in the treatment of intractable pain. Occasionally the side effects of a given drug may be so marked as to limit its usefulness. In large doses, usually associated with prolonged administration, phenothiazine derivatives may produce toxic effects on the liver or bone marrow.

USE IN OBSTETRICS

Chlorpromazine and promethazine have been used as calming agents and to potentiate analgesic drugs in the first stage of labour. Chlorpromazine produced marked calming and potentiation of analgesics, but prolonged labour and increased the incidence of forceps delivery, probably through reduction in smooth muscle tone. Fetal respiration was not depressed and no adverse effects were observed in the third stage of labour.[5, 6]

Promethazine showed little calming, and potentiated analgesics poorly. Its effect on the length of labour was not stated.[7] Intravenously promethazine may produce respiratory depression, though in this series the fetal respiration was unaffected.

Both drugs were unpredictable in their effects, even when given intravenously, and both produce hypotension, which is occasionally marked.

Mepazine (Pacatal) (N-methylpiperidyl-3-methylphenothiazine) is claimed to possess good calming and potentiating activity with minimal vascular and autonomic effects, and has previously been used in the second stage of labour with no adverse effects on the fetus.[6] A preliminary trial is reported here in which the calming and potentiating activity of Pacatal during the first stage of labour has been assessed, and the magnitude of its side-effects estimated.

MATERIAL

Initially the trial was limited to those patients with the fetus presenting by the vertex, with the head engaged, and in whom labour had begun spontaneously or followed medical induction at or near term. Later, Pacatal was also given to patients in prolonged labour, since such cases provided the most difficult problems of analgesia. No case with toxæmia of pregnancy or with complicating medical disease was included. In order to provide uniform assessment, no case was admitted to trial which could not be supervised continuously throughout labour by the observer, who was responsible for the timing and dosage of Pacatal and other agents. The additional agents used were restricted to Demerol (meperidine), sodium Amytal, nitrous oxide and oxygen, and trichlorethylene (Trilene).

At a preliminary trial, no statistical deductions were made from the observations and no controls were used, attention being directed to determination of dosage, sedation, potentiation, and vascular and autonomic effects. In all the drug was given on 44 occasions to 25 patients, 15 receiving it by the intravenous and 10 by the oral route; 22 were primigravidæ and three multigravidæ. The fetal lie and presentation on admission to the trial was vertex occipito-anterior in 17, vertex lateral or posterior in seven, and breech left sacro-anterior in one. One patient with cervical dystocia was admitted to trial after 28 hours in labour.

OBSERVATIONS

Dosage.—The drug was diluted to an 0.5% solution in distilled water, the only compatible diluent. To determine the effective dose, intravenous injection of doses ranging from 25-200 mg. was given to patients who had no previous medication, taking two to three minutes to inject. After injection of an effective dose the patients would become calm and drowsy, the maximum effect appearing in five minutes, when the patient appeared to be asleep but responded readily and rationally when spoken to. Although these effects would appear to have an indefinite end-point, in practice there was little variation in the determination of an effective dose in individuals, which appeared to be 1 mg. per lb. of body weight. Larger doses produced no greater effect and the effects were reproducible fairly constantly by the oral route in similar dosage, though taking longer to appear. The effects of the drug were more

evident with distressed patients than with co-operative patients, but during contractions both groups showed that Pacatal had no significant analgesic action. Therefore patients who would normally have received 100 mg. doses of meperidine were given 50 mg. doses intramuscularly, and this gave satisfactory relief. Patients with severe pain during the course of a long labour, when a settling dose of morphine would usually have been necessary to secure rest, were well relieved and able to sleep on the combination of 150 mg. Pacatal and 100 mg. meperidine.

Barbiturates were also potentiated and a satisfactory hypnotic effect was achieved by the combination of 3 grains sodium Amytal and 100 mg. Pacatal. Nitrous oxide and oxygen and trichlorethylene analgesia was not markedly potentiated, but five patients admitted in late first-stage labour received Pacatal and inhalational agents only and had good relief.

Effect on uterine contractions.—The duration and frequency of uterine contractions was observed for a 30-minute period after the intravenous injection of an effective dose of Pacatal in five patients. Two of these patients were primigravidæ in very early labour having contractions every 10 minutes, and the cervix was not dilated or taken up. In all cases uterine contractions increased in frequency and duration, and appeared more painful. This does not imply that the contractions had become more effective, though the subsequent course of labour suggested they were.

However, Pacatal did appear to potentiate the effect of meperidine in reducing the frequency and duration of uterine contractions when meperidine was given in usual doses, particularly before two-finger dilatation of the os. When the dosage of meperidine was reduced or when labour was well established, this effect was not marked.

Labour ceased in one patient eight hours after receiving an effective dose (100 mg.) of Pacatal and 100 mg. meperidine in early labour, but the drugs are not thought to have been responsible for this effect.

Vascular effects.—The blood pressure was recorded at 2½-minute intervals for 30 minutes after an intravenous injection of Pacatal on 13 occasions, with the patients in the supine position. At the end of this time the patients were placed in a sitting position and the blood pressure recorded for a further 10 minutes. The systolic blood pressure fell in six supine patients (average fall 12 mm. Hg; greatest fall 25 mm. Hg), remained unchanged in one supine patient, and rose in four supine patients (average rise 8 mm. Hg). In all sitting patients the blood pressure rose (average rise 5 mm. Hg). The diastolic pressure was not recorded. There were no symptoms referable to blood pressure changes in any of these patients. The pulse rate usually remained unchanged or slowed, and some vasodilatation of skin was observed. Pacatal had no discernible effect upon the fetal heart rate.

Other autonomic effects.—Dryness of the mouth and a tendency to nasal congestion were noted in most patients but few complained of it. Loss of accommodation was not noted. Nausea occurred in three patients, two of whom vomited about 10 minutes after receiving intramuscular meperidine.

Second stage.—Patients rested well between pains and were extremely co-operative, with two exceptions. One of these responded to firm reassurance, but the other, a patient in whom labour was prolonged, had been given large doses of sedation to secure rest. Rapid dilatation occurred, and the patient was confused and uncontrollable during the second stage, requiring anæsthesia for delivery.

About half the patients required nitrous oxide and oxygen analgesia at the close of the second stage. The average duration of the second stage was one hour and five minutes.

Of the cases of lateral or posterior positions, three heads rotated spontaneously and were delivered occipito-anterior, two were delivered spontaneously face to pubis, and two were manually rotated and delivered by forceps under general anæsthesia. Forceps delivery for fetal distress was performed in one patient where the fetus was occipito-anterior, with the cord tightly round the neck.

Third stage.—The uterus contracted and the placenta separated normally without undue delay. Ergometrine was given only when the loss seemed excessive, or with the anterior shoulder in forceps delivery. The average duration was 15.2 minutes and the average loss 12.8 oz. There were four cases of postpartum hæmorrhage, whose average loss was 25.5 oz.; none required transfusion. No manual removals of placenta were performed.

State of the infant.—The majority of infants appeared very active and were quick to breathe even when Pacatal had been given within one hour of delivery. Three babies cried vigorously before delivery of the trunk. Three showed blue asphyxia but were reflexly active and responded to an oxygen atmosphere. The remainder required no resuscitation. The average time to the first cry was 18.8 seconds, and to the onset of regular normal respirations 14.7 seconds.

Assessment of analgesia.—During labour additional analgesia was given when the patient appeared distressed or asked for relief. The subjective assessment of the patient after labour is altered by factors of relief and new-found motherhood, and may be adversely affected by the physiological depression which follows delivery. There are further difficulties in classifying degrees of pain. Accepting these limitations, the patients were visited within 36 hours of delivery and asked to select the most appropriate of two or three alternatives under the headings of labour, the pain experienced at the worst moments, the

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TABLE I.

	Labour			*Pain*			*Drugs*		*Next pregnancy*	
	Better	*As expected*	*Worse*	*Mild*	*Severe*	*Unbearable*	*Enough*	*More*	*Yes*	*No*
Primigravidæ...	9	5	5	3	9	7	10	9	17	2
Multigravidæ...		(as before: 1)	1		2		1	1	2	

drugs given, and their attitude to the next pregnancy. The results are shown in Table I. In addition they were questioned as to their memory of events, and the amnesia was graded as none, slight, or marked, by the observer. Slight amnesia was recorded when the patient could remember being moved into the labour ward and the birth of the baby, but had little recollection of other events. Marked amnesia was recorded when these events had been forgotten, or when there was a period of apparent consciousness exceeding three hours of which the patient had no memory. Marked amnesia was recorded in nine primigravidæ, slight amnesia in six, and none in four; there was slight amnesia in one primigravida and none in one.

Complications and toxic effects.—Local phlebothrombosis occurred at the injection site in two patients receiving Pacatal intravenously. Aching pain in the vein immediately following intravenous injection occurred in six patients. The intravenous route was therefore abandoned in favour of the oral route later in the trial. This proved equally effective. No cases of toxic jaundice or agranulocytosis occurred.

CONCLUSIONS

The calming effect of Pacatal is valuable in first-stage analgesia, especially in primigravidæ and in those patients inaccessible to reassurance because of the nature of their personalities or because of language difficulties. It can be freely given in the early part of labour without depressing uterine contractions, and in the later stages of labour its potentiation of analgesics and hypnotics enables a desired effect to be achieved with smaller doses than would otherwise have been necessary. It has no depressant effect upon the reflex activity of respiration of the infant, so that with these smaller doses of analgesics the infants tend to be more active at birth.

In this group of healthy young adults the compensatory reflexes were sufficiently active to counteract any hypotension produced by Pacatal, so that no symptoms referable to hypotension arose, and the fetus appeared unaffected.

The potentiation of the depressant effect of meperidine upon the uterus was not marked, and provided ordinary care was used in the assessment of the patient's need for meperidine, by reserving it until strong and frequent contractions were present or until the cervix was two-fingers dilated, the combination of agents did not appear to alter the course of labour.

Pacatal is a tissue irritant on intravenous or intramuscular injection; since it is equally effective by mouth, the oral route should be chosen.

SUMMARY

Mepazine (Pacatal) (N-methylpiperidyl-3-methylphenothiazine) was given to 25 patients in the first stage of labour. The patients were calmed, and analgesics and hypnotics potentiated. Side-effects were mild and uterine contractions increased in frequency and duration after its use.

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RÉSUMÉ

L'effet sédatif de la mépazine est utile dans l'analgésie des premières douleurs de l'accouchement, particulièrement chez les femmes enceintes pour la première fois et chez celles qu'il est impossible de rassurer soit à cause de leur personnalité ou à cause de leurs difficultés à s'exprimer. On peut l'administrer au début du travail sans craindre une diminution des contractions utérines. Au cours du travail même, il renforce l'action des analgésiques et des hypnotiques et permet d'atteindre l'effet désiré tout en employant une dose réduite de médicament. Il ne déprime aucunement l'activité réflexe et respiratoire de l'enfant, de sorte qu'avec des doses d'analgésique plus petites, l'enfant est plus éveillé à sa naissance.

Dans le groupe des 25 jeunes femmes normales étudié ici, les réflexes vasculaires compensateurs furent suffisamment actifs pour remédier à la chute de tension artérielle produite par la mépazine et aucun symptôme attribuable à l'hypotension ne fut noté. Les enfants n'en semblèrent pas affectés non plus.

L'effet déprimant de la mépéridine sur l'utérus fut très peu accentué par la mépazine. A condition que le besoin de la parturiante pour la mépéridine soit bien compris, c'est-à-dire en ne l'administrant que lorsque les contractions sont fortes et fréquentes ou lorsque la dilatation du col atteint au moins la pièce française, la combinaison de ces deux agents ne semble influencer nullement l'évolution du travail. La mépazine est un irritant pour les tissus tant par administration intraveineuse qu'intramusculaire; puisqu'elle agit bien par la bouche, c'est ce mode d'administration qu'il convient d'employer.

INTRAVASCULAR AGGLUTINATION AND C-REACTIVE PROTEIN

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IT IS WELL KNOWN that the erythrocyte sedimentation rate can be correlated in some degree with intravascular agglutination.[1] The erythrocyte sedimentation rate is also roughly comparable in certain disease states to the C-reactive protein.[2] With these facts in mind it was decided to attempt a comparison of intravascular agglutination and C-reactive protein.

Intravascular agglutination, or "sludged blood" as it was termed by Knisely,[3] is the clumping of erythrocytes into "basic masses" and "aggregates" of these masses. Sludging occurs in a wide range of disease states including trauma, inflammation, infestation, malignancy, infarction, and collagen diseases. In fact, completely unagglutinated blood has been found only in strictly healthy animals and men, and has even been found in normal uncomplicated pregnancy.[4] Its gross effects were observed in 1786 by John Hunter,[5] who pointed out in a lecture to students that in inflammatory conditions drawn blood had "an increased disposition to settle into its component parts, and when spreading over a surface it appears mottled, the red blood [cells] attracting itself, and forming spots of red". In 1858 and 1869, Lister[6] published papers in which he described direct microscopic observation of precipitation and agglutination of blood flowing through crushed tissues. In the early 1920's studies of the capillary bed were revived by Krogh and the suspension stability of blood was discussed by Fahraeus[6] (whose observations led to the erythrocyte sedimentation rate). In November 1944, Knisely and Block[6] presented the first of a large series of papers from their laboratory on intravascular agglutination studies in humans.

Knisely describes many kinds of blood sludges that may be observed in the peripheral circulation. In homogeneous sludges all the red cells are in masses of approximately the same size and rigidity. In mixed sludges, free unagglutinated cells may be present, or several sizes of basic masses may be present simultaneously. There are those in which most basic masses are small, but larger masses come along at intervals, plugging the arteriole they enter. There are sludges composed of masses which repel each other slightly, and others in which the masses come together, sometimes from a distance, producing aggregates. In certain sludges the basics and aggregates seem sticky and adhere to one another; others appear coated with glassy hard materials and display no tendency to adhere to each other. Some sludges are bright red, with little if any material between and around the red cells; and there are others in which the masses are pale pink and, when they bump each other, behave as though a transparent invisible layer was around the red cells in each mass extending beyond the red cells.[7]

Since under normal conditions red blood cells do not appear to be coated with any substance and do repel one another, presumably by electrical charges, it may be assumed that some sludges are due to coating of the erythrocytes by altered or abnormal blood proteins, as has been shown to occur in stage III of Knowlesi malaria in monkeys,[8] while others are possibly due to alteration of the surface charges of the red blood cells.

C-reactive protein is an alpha globulin, undetectable in health but appearing promptly in the course of a wide variety of diseases. It forms a precipitate with C polysaccharide of pneumococcus (to which reaction it owes its name) and is serologically distinct from normal serum proteins. In its detection, equal parts of the patient's serum and rabbit antiserum to C-reactive protein are mixed in a capillary tube, followed by appropriate incubation. The results are based on the amount of precipitate in the tube.[8]

METHODS AND MATERIALS

The erythrocyte sedimentation rate was determined by the Wintrobe method (normal: males 0-10; females 0-20) and the C-reactive protein by the capillary tube precipitin technique in the Hæmatology Laboratory of the University of Alberta Hospital. The commercial serum used in the procedure was obtained from the William Schieffin Company.

An American optical binocular microscope on a swing-arm mounting with magnifications from 60 to 120 to 150 was used for observation of the degree of sludging. Oblique illumination from a small lamp containing heat-absorbing filters was used, the lamp having been conveniently mounted on the body of the microscope.

Thirty-nine adults, in-patients of the University of Alberta Hospital, were selected on the basis of diagnosis as suitable for this study (several others were rejected because of inability to co-operate or local ocular disease.) They were examined supine, the microscope and lamp swung over their head, the eyelids gently retracted, the light focused and the bulbar conjunctiva observed. Multiple observations were made on the last 11 of these, so that 55 comparable observations in all were made. The middle power of the microscope was found the most satisfactory; the highest afforded poor resolution and too much interference due to eye movement and vibration.

CRITERIA USED IN THIS STUDY

The C-reactive protein results were reported by the laboratory in seven degrees, from negative to six-plus. The degree of sludge was divided into four categories:

1. Negative—no aggregation, no stasis, no segmentation of flow; even flow of individual red cells; therefore, single red blood cells could not be seen in vessels larger than capillaries.
2. Minimal—smallest discernible aggregates, even flow in larger vessels (arterioles and venules), some minimal segmentation of smaller vessels and obstruction of capillaries for one to two seconds only.
3. Moderate—larger aggregates, with even flow in

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TABLE I.

Patient	*Diagnosis*	*Sludge*	*C-Reactive Protein*	*Correlation*
Mr. L.W.	Rheumatic heart disease	Min.	neg.	Good
Mr. H.	Cardiac infarction	Min.	neg.	Good
Mrs. L.	Arteriosclerosis, electrolyte imbalance	Mod.	neg.	Poor
Mr. R.N.	?	Min.	neg.	Good
Mrs. L.	?	Min.	neg.	Good
Mr. H.	Carcinomatosis (stomach)	Mod.	3 plus	Good
Mrs. G.	Rheumatic fever (active)	Max.	4 plus	Good
Mr. E.	Chronic nephritis and hypertension	Mod.	1 plus	Poor
Mrs. Y.	Anxiety	Min.	neg.	Good
Mrs. G.	Segmental colitis	Max.	3 plus	Poor
Mr. L.W. (as above)	Rh. fever and subacute bact. endo.	Mod.	4 plus	Good
Mr. P.	Collagen disease	Mod.	3 plus	Good
Mr. M.	Cardiac infarction	Max.	4 plus	Good
Mrs. St.M.	Anxiety—Trichomonas vaginitis	Min.	neg.	Good
Mrs. H.	Old rheumatic heart disease	Mod.	neg.	Poor
Mr. L.	Gout	Mod.	2 plus	Good
Miss F.	Schizo-affective disorder	Min.	neg.	Good
Mr. S.	Cardiac infarction	Max.	neg.	Poor
Mr. M.D.	Rheumatic carditis	Mod.	5 plus	Poor
Mr. McC.	Cardiac infarction	Max.	neg.	Poor
Mr. A.McD.	Cellulitis foot	Min.	6 plus	Poor
Mr. R.C.	Acute coronary insufficiency	Max.	5 plus	Good
Mr. J.P.	Carbuncle rt. hip	Mod.-Max.	2 plus	Good
Miss P.B.	Upper respiratory infection	Mod.	2 plus	Good
Mrs. L.S.	Pneumonia (1 week)	Mod.	neg.	Poor
Mrs. M.B.	Multiple abscesses (3 months)	Mod.	neg.	Poor
Mr. K.E.	Cellulitis face (1 week) and diabetes mellitus	Min.	3 plus	Poor
Mrs. J.H.	Pneumonitis	Min.	neg.	Good

large vessels, reduced rate of flow in smaller vessels; aggregates bumping through capillaries with "temporary obstruction"; that is, flow with each arteriolar pulsation and occasional reversal of flow.

4. Maximal—capillary obstruction, further reduction in rate of flow in larger vessels, occasional temporary obstruction of larger vessels, conjunctival œdema; and when very severe, "porridge-like flow" of blood.

TABLE II.

Patient	*Diagnosis*	*Date*	*Erythrocyte sedimentation rate*	*WBC*	*Sludge*	*C-reactive protein*	*Correlation*
Dr. F.M.	Cardiac infarction	Feb. 27	24	21,350	Max.	6 plus	Good
		Mar. 7	43	7750	Mod.	2 plus	Good
		Mar. 13	39	10,200	Mod.	2 plus	Good
Mrs. J.B.	Diabetes mellitus, bronchopneumonia	Mar. 7	35	9900	Mod.	5 plus	Poor
		Mar. 13	47	8750	Mod.	neg.	Poor
		Mar. 19			Min.	neg.	Good
Mr. E.F.	Diabetes mellitus, cold, and infected nose, cirrhosis	Mar. 13	33	11,250	Mod.	2 plus	Good
		Mar. 16	42	7900	Min.	2 plus	Good
Mr. H.C.	Acute glom. nephritis	Mar. 16	23	7150	Mod.	1 plus	Poor
		Apr. 3	37	7850	Min.	neg.	Good
Mr. J.H.	Myocardial infarction	Apr. 6	48	12,250	Mod.	5 plus	Poor
		Apr. 14	51	9000	Mod.	—	
	Extension	Apr. 20	47	6250	Max.	4 plus	Good
		Apr. 29	59	8300	Min.	2 plus	Good
		May 2	60	—	—	2 plus	
Mr. A.P.	Probably myocardial infarction	Apr. 6	31	6950	Mod.	neg.	Poor
		Apr. 14	25	6750	Mod.	neg.	Poor
		Apr. 20	22	—	Min.	neg.	Good
		Apr. 29	18	7250	Min.	neg.	Good
Mrs. A.M.	Arteriosclerosis, recurrent bronchitis and pyelonephritis	Apr. 6	57	10,450	Min.	3 plus	Poor
		Apr. 14	58	11,850	Min.	4 plus	Poor
Mr. W.H.	Abscess left ankle (2 mo.)	Apr. 29	43	7700	Mod.	1 plus	Poor
		May 4	42	—	Min.	neg.	Good
Mrs. J.T.	Discectomy (Mar. 2/56) with post-op. bacteræmia and metastatic abscesses	Apr. 29	58.5	7500	Mod.-Max.	3 plus	Good
		May 4	61	—	Mod.	3 plus	Good
Miss L.F.	Bronchopneumonia	Apr. 29	52	4850	Mod.	neg.	Poor
		May 4		6850	Min.	2 plus	Good
Mr. D.T.	Rheumatoid arthritis and cholecystitis (3 weeks)	Apr. 29	47	9750	Max.	4 plus	Good
		May 4	50	—	Mod.	2 plus	Good

No negative observations were made, the most common being minimal and moderate.

RESULTS

In a preliminary study, single observations were made on a series of patients on whom C-reactive protein was being determined. The results are shown in Table I.

Since some correlation was obtained in the preliminary study, the illnesses of 11 patients were followed. Observations of intravascular blood flow and C-reactive protein determinations were carried out on the same day and repeated at appropriate intervals. The results are contained in Table II.

DISCUSSION

With some exceptions the degree of red cell agglutination correlates well with the C-reactive protein determination when they are grouped thus:

Sludge	
Neg.	C-Reactive protein: 0
Minimal	neg. 1 plus, 2 plus
Moderate	2 plus, 3 plus, 4 plus
Maximal	4, 5, and 6 plus

In the preliminary study, 17 out of 28 or 60.7% of the observations correlated. This agrees well with the second or multiple observation series in which 17 out of 27 or 63% correlate.

There are some exceptions (for example, Mr. MacD. in Table I: Max.—neg.) in which no correlation whatever is observed. These cannot be explained at the present time. As our knowledge of these apparently related phenomena increases, the explanation may become obvious.

C-reactive protein is obviously a result of the bodily reaction to the disease states in which it occurs and may be a defence reaction. Intravascular agglutination falls easily into the former category but not so well into the latter. Knisely lists four general ways in which sludging damages the body: forcible reduction in rates of blood flow in all open vessels, ingestion and destruction of agglutinated red blood cells by phagocytic cells of liver and spleen, sedimenting of masses out of plasma during life (thrombosis), and vasomotor shutting off of flow in certain tissues as a result of reduced blood volume. It seems evident that red cell agglutination is not a beneficial reaction.

Until the kind or kinds of protein that coat the red cells in certain sludges is accurately determined, we are unable to state whether the two phenomena discussed here are causally or incidentally related.

SUMMARY

A parallel study of intravascular erythrocyte agglutination and C-reactive protein has been made and some correlation found. The nature and possible interrelationship of these is discussed.

This work was done on the wards of the University of Alberta Hospital in 1955 and 1956 while the author was a junior assistant resident. It was done under the direction and guidance of Dr. R. C. Harrison, F.R.C.S., Associate Professor of Surgery, University of Alberta.

The author wishes to acknowledge the invaluable assistance of Dr. R. E. Bell, Director of Laboratories, University of Alberta Hospital.

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RÉSUMÉ

On a cherché ici à établir une comparaison entre l'agglutination intravasculaire et la présence de protéine C réactive. Le premier phénomène consiste en la formation de masses d'érythrocytes groupés qui donnent au sang un aspect boueux et en augmentent considérablement la viscosité. Lorsqu'il se produit dans les vaisseaux, ce phénomène peut causer de sérieux troubles circulatoires. La protéine dite "C réactive" est une alpha-globuline apparemment absente chez l'homme en santé et qui précipite en présence d'un polysaccharide (C) du pneumocoque.

Un total de 55 observations furent faites sur 39 sujets porteurs d'affections diverses. L'intensité des deux phénomènes fut graduée d'après des normes établies par l'auteur. L'étude des résultats montra une corrélation satisfaisante dans 60.7% des cas, indiquant que ces phénomènes se trouvent simultanément dans un bon nombre de circonstances. Un revêtement protéinique des hématies serait la cause de l'agglutination. Il est encore impossible d'affirmer que la fraction protéinique en jeu soit celle de la protéine C réactive.

INFLUENCE OF GONADAL HORMONES ON SERUM LIPIDS AND LIPOPROTEINS

High density serum (alpha) lipoproteins and the ratio of high density to lower density (alpha/beta) lipoproteins are sensitive indicators of change in gonadal hormone relationships. Increase in relative œstrogenicity, whether by administering œstrogen or withdrawing androgen, is always associated with increase in high density lipoprotein concentrations and in high density/low density lipoprotein ratios. Increase in relative androgenicity has the opposite effect. The lower density (beta) lipoprotein response is more variable but usually opposite to that of the high density fraction.

Changes in chemically determined cholesterol and phospholipid levels appear to be determined by the nature of the changes in the major lipoprotein fractions under these conditions. On the other hand, absence of change in serum cholesterol or phospholipid levels does not preclude the possibility of major alteration of the lipoprotein spectrum.

Whether these serum lipoprotein-hormone relationships are causally related to the *marked sex difference in the incidence of coronary artery disease* remains to be determined. There is good agreement that the concentration and physical status of the serum lipids have some etiologic significance in this disease. Further efforts in the direction of the studies described are warranted.—R. H. Furman and P. R. Howard: *Ann. Int. Med.*, 47: 969, 1957.

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THE PLACE OF EARLY INDUCTION IN THE MANAGEMENT OF ERYTHROBLASTOSIS FETALIS*

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IT IS NOW POSSIBLE to know beforehand in nearly every instance that a particular baby is going to have hæmolytic disease when it is born. It is also possible to treat successfully nearly all such babies who are born alive. The remaining immediate problem is the problem of stillbirth. What can be done about stillbirths due to Rh sensitization? The broad answer is that some proportion of babies who would otherwise die before birth can be saved by early termination of pregnancy. But against savings that may result from early termination one must set the risk of loss due to premature delivery. One must select for early delivery those who, allowed to go to term, would have a poor chance of survival. On what basis can such a selection be made, and, the selection having been made, what hope can be offered of a successful outcome?

In estimating the prognosis for a current or future pregnancy the history of the outcome of previous pregnancies is the *most* important information that you can have. Antibody titrations do help in some cases but the history is *most* important. I therefore show you here first in Figs. 1 and 2 an estimate of prognosis based on history alone. I draw your attention particularly to the bad prognosis for future Rh-positive babies once a mother has given birth to a baby severely ill at birth with erythroblastosis, and the still worse prognosis if she has had one or more stillborn babies in whom death has been proven to be due to erythroblastosis. Just a word here. Pathologists as a whole appear to be repelled by stillborn babies; examination of the body is likely to be cursory, information obtained from a postmortem almost nil. But this need not be so. A fetus who dies of erythroblastosis almost always carries a triad of pathological signs, namely, a small thymus, a large spleen, and deposits of lipoid in a deep fetal cortex of the adrenal. These are signs which can be seen in quite a decomposed fetus if the pathologist will but look for them, and if he has scales that weigh small quantities accurately, and uses them. Microscopic examination is not necessary. There is another simple test that can be applied post mortem; the great vessels of the fetal surface of the placenta for several days after a fetus dies contain clots in which the red cells of the fetus are well preserved. Save the placenta in every stillborn fetus—*not* in formalin—and have the pathologist extract and test these cells by the direct Coombs method; a positive reaction indicates that an antibody from the mother has crossed the placenta and attached to the red cells of the fetus; it has had some degree of erythroblastosis; the indications are there for a more careful examination of the body, looking for the triad I have mentioned. Finally in every stillbirth it is always possible to check the mother's blood against that of the father, looking for Rh or other incompatibility.

Degree of disease at birth	*Class*	*Frequency in first pregnancy with antibodies*
Well at birth. No treatment.....	A	70
Appear well. But Hb down; bilirubin up. Untreated develop severe jaundice.....	B	23
Appear really ill. Severe anæmia. Untreated die first day.....	C	1
Hydrops or stillborn.....	D	6

Fig. 1.—Prognosis in first sensitized pregnancy.

If most severe disease in any baby has been.....		Chances for next baby are			
	A	A 60	B 30	C 5	D 5
	B	10	60	15	15
	C		5	35	60
	D		1	9	90

Fig. 2.—Prognosis from history.

Why is it desirable, indeed necessary, to go to this trouble to establish the presence or absence of erythroblastosis in a dead fetus? Because it is going to make all the difference in your advice to the parents; it is going to make all the difference in what you do when the mother of that dead fetus becomes pregnant again; it can make the difference between life and death of the baby in a future pregnancy. The fetus of an Rh-negative woman may die from causes other than erythroblastosis. If you assume but do not prove that death has been due to this disease and are wrong, you may later be led to radical action which may result in the death of another fetus where no such radical action was necessary.

If then a woman has had one fetus die of erythroblastosis, or one fetus born with hydrops, the chances are 9 out of 10 that the next Rh-positive fetus will die before the 40th week. If a woman has had two fetuses die of erythroblastosis or one die and one born with hydrops, the chances are that almost 100% of future Rh-positive fetuses will die of erythroblastosis before the 40th week. If it can be proved, or if there is a high probability, that the husband of such a woman is homozygous Rh-positive and therefore can father only Rh-positive children, I think it is mandatory that you be prepared to deliver the woman early if the fetus lives beyond the 32nd week and is well grown for its age. If the husband is heterozygous you have a

*Presented at the Ninetieth Annual Meeting of the Canadian Medical Association, Edmonton, June 1957. From the Rh Laboratory, 735 Notre Dame Ave., Winnipeg 3, Manitoba, and the Department of Pædiatrics, University of Manitoba.

more difficult decision to make: if the fetus is Rh-positive and you do not interfere it will almost surely die; if it is Rh-negative it will not have erythroblastosis; if you induce labour, what is the prognosis for survival of a 3 or 4 lb. baby in the hospital in which the woman will be delivered? There is the balance: practical certainty of death for the Rh-positive fetus weighing against what chance for survival of an Rh-negative premature?

If the father is heterozygous, can one foretell whether a given fetus is Rh-positive or Rh-negative? Occasionally, but only occasionally, you may obtain information of value by having periodic titrations of the mother's Rh antibodies done: a rising titre almost always indicates that the fetus is Rh-positive; a steadily falling one that it is Rh-negative, but unfortunately in most cases the antibody level remains constant and tells you nothing. Amniotic fluid has been investigated. Witebsky *et al.*[1] reported that small quantities of Rh substance in soluble form occurred in the amniotic fluid of Rh-positive fetuses except those who had erythroblastosis; obviously there is no help in this observation. Freiesleben *et al.*[2] examined the sediment in amniotic fluid removed by paracentesis; they could determine the ABO group but not the Rh type of the baby by such an examination; again there is no help here. Bevis of Manchester,[3] examining amniotic fluid obtained by paracentesis, was able to show that in the sick infant bile pigments and heme pigments appeared in the amniotic fluid, and that when the latter pigments were demonstrable the probability of fetal death was high. This method is promising but it is still in the early stage of development. Blanchaer and I[4] have carried out measurements of certain red cell enzymes in the plasma of the fetus at birth and that of its mother, hoping that an elevation in the fetal plasma would be mirrored in the maternal; there was no such mirror image.

I have illustrated for you the general prognosis in erythroblastosis, laying emphasis on the conditions under which fetal death is likely to occur, and I have said that some proportion of these fetal deaths may be prevented by early termination of pregnancy. Whether or not you can save the life of a fetus depends in part on how long it lives. I do not believe that anyone would attempt termination of pregnancy before 32 weeks and expect to get a child who would live, so that in giving a prognosis it is important to know first of all what proportion of babies who are going to die *in utero* will have died by this time. The best information we have on this at present, derived from the excellent studies of Walker, Murray and their associates[5] and from our own experience, is set out in Fig. 3. From this you can see that in the group in which you might possibly consider early induction about 25% of those who are going to die before term will have died before 32 weeks; you cannot then prevent 25% of the deaths. To have a chance of saving those who would otherwise die it is necessary to terminate labour at 34 to 36 weeks for the woman who has a history of one baby stillborn because of erythroblastosis, and at 32 to 34 weeks for the woman who has a history of more than one stillbirth due to erythroblastosis. Among the babies so born prematurely you may expect to save by expert treatment 75 to 90%.

Time of death	*No. of previous stillbirths*	
	1	*More than 1*
% before 32 weeks	15	30
% 32–37 weeks	30	40
% 37–40 weeks	45	29
Live-born at term	10	1
Degree of disease in live-born	B 1 C 9	C 1

Fig. 3.—Probability of fetal death following proven erythroblastotic stillbirth.

Such a program as this is not to be undertaken lightly and should be carried out only in hospitals expert in the care of such babies, for you will be faced with a baby who is both premature and sick, often very sick. These babies always require replacement transfusion and not infrequently two, three or four replacement transfusions if they are to be saved and if kernicterus is to be prevented. My own recommendation is always to seek the advice and assistance of an obstetrician; one must always take into consideration the apparent size of the fetus and the state of the cervix, and the probability of effective labour ensuing. There does not appear to be any one proven way of termination of pregnancy which is certainly better than another. Medical induction will practically always fail. Some believe that a preliminary course of intravenous pitocin makes a labour after surgical induction more certain. Our own practice has been to do a surgical induction with or without preliminary pitocin and if necessary followed by pitocin, and if active labour does not ensue by 48 hours after rupture of the membranes then to do a Cæsarean section; section has rarely been necessary. During labour the services of an expert anæsthetist are a great asset; you are dealing with a fetus already ill, often very ill, and a skilful anæsthetist can do much to support rather than depress the fetus. Equally an expert anæsthetist may be valuable in the resuscitation of a sick baby immediately after birth.

I am well aware that early induction of labour was widely tried some years ago and was abandoned; many of the babies developed kernicterus and either died or were left with cerebral palsy. I am not recommending to you indiscriminate early induction, but induction in carefully selected cases where the prognosis for a live birth is poor. In such cases early induction can save life; a woman can give birth to a live baby instead of a dead one. To keep that baby alive and to prevent its developing kernicterus requires the most painstaking and expert care for the next 24 to 72 hours, including one, two, three or even four replacement transfusions.

Seep. Rr.

1	2	3	4	5	6	7	8
R.	r.	I.G. Died	Hb. 12.8 / Bili. 4.6	9.8 / 5.9	11.2 / 4.9	11.1 / 3.5	10.2 / 5.56

All received replacement transfusion stat.

Prognosis
1. Always 50% chance Rh-negative
2. For Rh-positive:
A 10
B 60
C 15
D 15

Fig. 4.—Icterus gravis not an indication for early induction.

In Figs. 4 to 7, RR after family name = homozygous Rh-positive husband; Rr, heterozygous. For the children R = normal Rh-positive; r = Rh-negative; I.G. = icterus gravis; H.F. = hydrops fetalis; Ect. = ectopic pregnancy; S.B. = stillborn. For the figures separated by a horizontal bar the upper represents the hæmoglobin in grams, the lower the bilirubin in milligrams per 100 ml., cord blood unless otherwise stated. The prognostic symbols A, B, C, D have the significance given in Figs. 1 and 2.

May I illustrate my thesis by some family records from our files? I show you first a family (patients of Dr. Donald Hastings) in which the third child died of icterus gravis (Fig. 4). From Fig. 1 you will see that the prognosis for Rh-positive fetuses in such a family is A 10, B 60, C 15, D 15, or a probability of a live birth at term in 85 out of 100. There is then little justification for early induction; the subsequent history in this family bears out this judgment, 5 live-born babies. The next family (patients, in later pregnancies, of Dr. J. Dougan) illustrates a change in prognosis and action based on that change (Fig. 5). The second child had erythroblastosis with fairly severe jaundice, but spontaneous recovery; it is mentally somewhat retarded. The prognosis for the next baby was as in the first family. The next three children were live-born but the third one was in class C, i.e. severely ill at birth, and was moreover this ill at 36 weeks, at which age it was spontaneously born. The prognosis for the next baby then became A 0, B 5, C 35, D 60, or even worse than this if one considered that had this baby not been born early it probably would have died *in utero*. Early delivery of the next baby was clearly indicated and was carried out with the result shown.

Lastly I show you two families with a very bad history and a final happy outcome (Fig. 6). The first was latterly a patient of Dr. R. A. Jacques of St. Boniface. You can see that the third baby had erythroblastosis with jaundice. The prognosis then was A 10, B 60, C 15, D 15 for the next fetus. Unlike our first family, in which succeeding babies continued in class B, in this family the next baby was in class D, and the prognosis became B 1, C 9, D 90. With the second hydrops (pregnancy 6) hope for a live-born at term became 1 in 100, with the expectation that it would be in class C, i.e. dangerously ill at birth. So it turned out for Baby No. 7, who died in spite of one replacement transfusion. Then followed 3 deaths, and then again the 1 in 100 chance, though fortunately this baby was born two weeks before term. It was a pale, puffy, œdematous baby. With three replacement transfusions by Dr. W. D. Bowman it survived. The patient is pregnant again; the prognosis for a live birth at term remains 1 in 100; for a treatable baby at 32 to 34 weeks about 50 in 100. The second family in this chart came under the care of Dr. Orville Hjertaas of Prince Albert for the woman's last two pregnancies. Fetus 8, like the earlier ones, died at about 6 months. When fetus 9 lived to an

Tall. RR.

	1	2	3	4	5		6
	R.	9 Days 14.8 / 22.8	11.4 / 2.8	13.3 / 3.45	4.0 / 5.0		2.8 / 4.9
		Jdce. Lessening Term ? 5^1	Replace 5 Hrs. Acct. Jdce. Term 6^8	Replace Stat. Term 7^2	Replace Stat. Spont. 36 w. 5^8		Replace Stat. Induct. 33 w. 4^1
Prognosis		A 10	10	10			
		B 60	60	60			
		C 15	15	15			
		D 15	15	15			
					A 0		A 0
					B 5	or	B 1
					C 35		C 9
					D 60		D 90

Fig. 5.—A Class C baby depresses prognosis: early delivery.

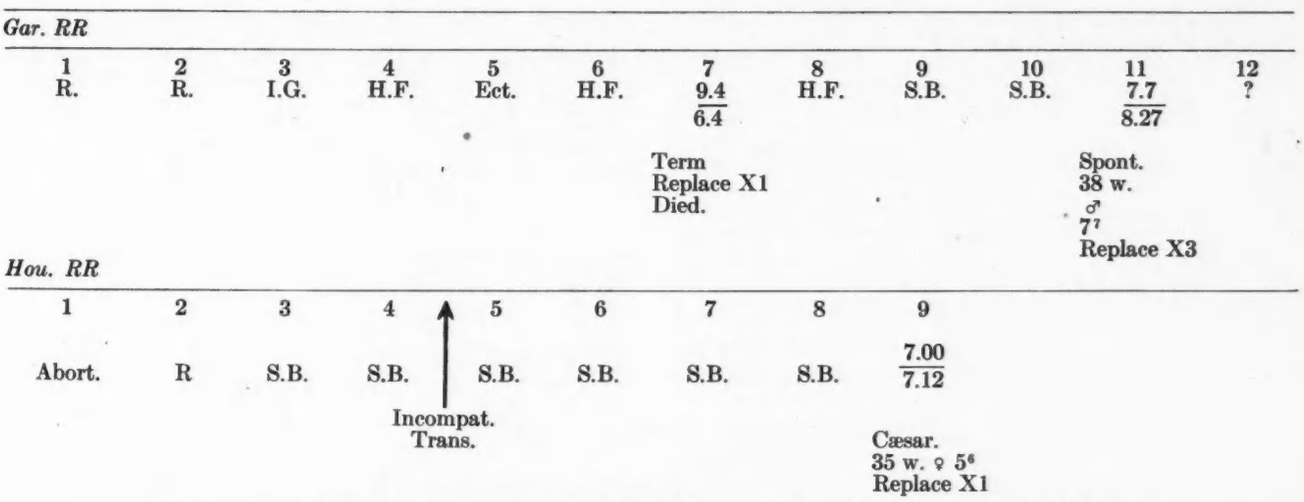

Fig. 6.—Hope of live-born at term after two stillbirths is 1 in 100: indication for early delivery.

estimated 35 weeks Dr. Hjertaas did a Cæsarean section and obtained for this poor woman a very ill but treatable baby girl, who made a good recovery following one massive replacement transfusion.

In our own service we believe that there is one additional indication for early induction of labour, namely a rapid and marked rise in the antibody titre. Believing this to be so, we go to a good deal of trouble with titrations, recommending that titration be carried out once a month to the seventh month and every two weeks thereafter. In most cases this gives us no added information, but every now and then we see a sudden rise in titre, recommend induction, and in a few cases believe that we have in this way been instrumental in preventing fetal death; two such are illustrated in Fig. 7.

Let me summarize briefly what I have said. The place of early induction of labour in the management of erythroblastosis is pre-eminently in those cases in which a woman has had one or more stillbirths due to erythroblastosis, or babies with hydrops, and whose husbands are homozygous Rh-positive. If there has been one example of fetal death from erythroblastosis or of hydrops, the chances are 9 out of 10 that the next Rh-positive fetus will die before the 40th week; induction at 34 to 36 weeks will save better than half of the babies who would otherwise die. If a woman has had two fetuses die of erythroblastosis or with hydrops, almost 100% of future Rh-positive fetuses will die before 40 weeks; by induction at 32 to 34 weeks you can save more than half that would die. Induction should be carried out in consultation with an obstetrician and in a hospital expert in the care of these babies. If they are not to die or suffer kernicterus after birth, they require the most meticulous care and treatment in the first 72 hours.

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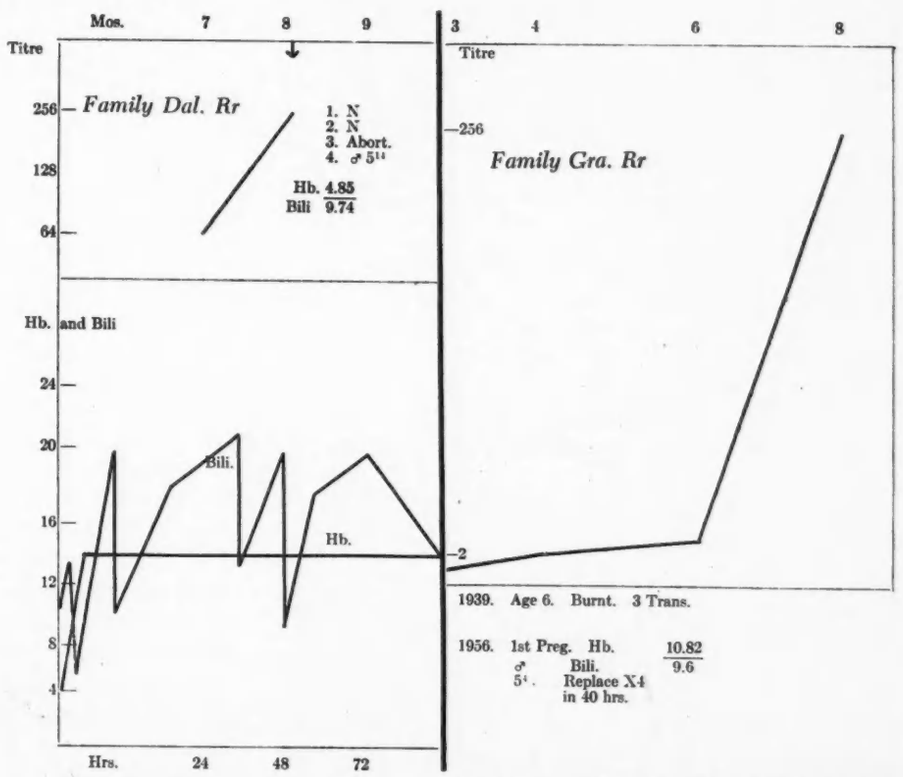

Fig. 7.—Graph at lower left gives bilirubin curve in detail, the four depressions being the lowering of the bilirubin concentration due to four replacement transfusions. The hæmoglobin line is an approximation for simplicity's sake. Figures on left hæmoglobin in grams, bilirubin in milligrams. This is the type of bilirubin curve one frequently sees in the baby who is delivered prematurely; to prevent brain damage or death one attempts to keep the bilirubin level below 20 milligrams.

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RÉSUMÉ

On peut souvent prédire la présence de l'érythroblastose fœtale de même que l'on peut soigner avec succès les enfants qui en sont atteints s'ils sont nés vivants. Le seul moyen qui n'ait pas été pleinement exploité en vue d'abaisser davantage la mortalité dans cette affection est de diminuer le nombre des enfants mort-nés. Le médecin doit choisir entre les risques de la prématurité en général et ceux que présente une grossesse à terme dans ces cas. L'évolution des grossesses antérieures forme la meilleure base sur laquelle on peut fonder le prognostic des grossesses futures. L'enfant d'une mère Rh négative peut succomber *in utero* à d'autres causes que l'érythroblastose. Il est donc essentiel d'obtenir une confirmation anatomo-pathologique des effets du facteur Rh chez tous les fœtus mort-nés. Les signes cardinaux que l'on peut observer à l'autopsie sont: un petit thymus, une grosse rate et des dépôts lipoïdiques dans les glandes surrénales. Le placenta peut aussi fournir des renseignements intéressants. Ces enfants se rendent difficilement à la quarantième semaine de la grossessse. Il a été établi par des études antérieures qu'à la trente-deuxième semaine de gestation, 25% de ceux qui doivent périr sont déjà morts. Il est presque toujours inutile à cette période de chercher à déclencher le travail par des moyens médicaux. Il faut avoir recours aux moyens chirurgicaux avec ou sans l'aide d'extrait de lobe postérieur d'hypophyse. Si 48 heures après la rupture artificielle précoce des membranes rien ne s'est encore produit, l'auteur recommande la césarienne.

THE ALBERTA PERINATAL MORTALITY STUDY*

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IN 1954 THE Canadian Medical Association, Alberta Division, set up a committee to investigate and review stillbirths and infant mortality in the province of Alberta.

At the outset it was recognized by the committee that a scientific study such as might provide statistically significant detailed figures on mortality and morbidity for the whole province would, to a great degree, be impossible because there are over one hundred hospitals in the province and only eight of the largest hospitals have a pathologist. In 1954 there were 876 perinatal deaths in Alberta. Over one-half of these occurred in hospitals that had no pathological services; consequently no autopsy examination was done on these cases and it was in most instances impossible to be sure of the cause of death. Just to gather information on each death that occurred in the province, where over 1000 medical practitioners are licensed, would be difficult.

It was therefore decided that the objective of the committee should simply be to encourage the hospitals, and the profession as a whole, to follow recognized obstetric and pædiatric principles in their care of pregnant women and their offspring. The committee was confident that, when this was done, the death rate would fall to a creditable level.

Selection of sample.—The committee at first considered studying stillbirths and neonatal deaths. This was found to be impractical because it was difficult to get a comprehensive story of the illness after the infant had left hospital. By limiting the study to those infants dying within the first seven days rather than the first 28 days, it was possible to get better records and still study the majority of these deaths. From Table I it can be seen that over 53% of the infants who die in the first year do so in the first seven days.

TABLE I.—INFANT DEATHS IN ALBERTA 1955

0 to 7 days	478	53.8%
8 to 28 days	61	6.9%
29 to 365 days	348	39.4%
Total	887	100.0%

In order to make sure that a report is received on every death it is necessary to be able to cross-check the cases reported to the committee with those registered at the Bureau of Vital Statistics. The Bureau of Vital Statistics' definition of a stillbirth is "a child who has never breathed and whose period of gestation is more than 28 weeks".[1]

It was therefore necessary to accept this as the definition of a stillbirth. The liveborn babies that are studied include all babies of 1000 g. (2 lb. 3 oz.) weight and over who die on or before their seventh day of life. Deaths in these two groups of babies comprise the perinatal deaths studied in Alberta.

Collection of data.—The committee first attempted to collect information on each death by having the mother's and infant's charts sent in from the hospital concerned. This procedure was quickly abandoned because the information needed was not on the charts. Instead of this a questionnaire* was made up which contains about 50 questions and which, when properly filled out, gives fairly complete information about the mother's previous pregnancies, her present pregnancy, her labour, the birth of the infant, the condition of the infant at birth, the investigation and treatment of the infant, progress notes and, finally, autopsy findings or cause of death or suspected cause of death. Each of these Alberta perinatal death forms requires about 12 minutes to fill out.

Organization.—In order to get the most value from the study of these perinatal deaths, for the profession as a whole, the hospitals in the province

*Presented at the Ninetieth Annual Meeting of the Canadian Medical Association, Edmonton, Alta., June 1957.
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*Copies of the Alberta Perinatal Death form are available on request to: The Perinatal Mortality Committee, Room 101, St. Joseph's College, University of Alberta, Edmonton, Alberta.

are divided into two groups: the urban section, in which each hospital has its own local committee to study its own perinatal deaths; and the rural section, in which each hospital sends its reports in to the central committee in Edmonton for review. In the urban group there are 10 local committees in five major cities in the province. Each local committee is composed of the physicians of that hospital who are doing obstetrics and pædiatrics, an anæsthetist and a pathologist. Each committee meets at regular intervals to study its own perinatal deaths and especially to ascertain if the case has been handled in an acceptable manner. The reports are then forwarded to the central committee for checking and tabulation. The same type of consideration is given by the central committee to each death that occurs in a rural hospital or any hospital without a local perinatal mortality committee. All the above information is punched on to keysort cards for filing.

Cause of death.—When a case is reviewed, either by a local or the central committee, an attempt is made first to decide on the cause of death. If no postmortem examination has been done this may be impossible. The following modification of Dr. Edith Potter's classification of cause of death is being used by the Alberta Perinatal Mortality Committee:

TABLE II.—CAUSE OF DEATH CODE

1. *Abnormal Pulmonary Ventilation*
   - (a) Hyaline membrane disease
   - (b) Atelectasis
   - (c) Unknown
2. *Birth Trauma*
   - (a) Intracranial hæmorrhage
   - (b) Other
3. *Malformation*
4. *Infection*
   - (a) Pneumonia
   - (b) Other
5. *Blood Dyscrasias*
   - (a) Hæmolytic disease
   - (b) Hæmorrhagic disease
6. *Anoxia* (due to maternal causes)
   - (a) Toxæmia
   - (b) Antepartum hæmorrhage
   - (c) Accidents to the cord
   - (d) Placental insufficiency
   - (e) Other
7. *Maternal Conditions*
   - (a) Infections
   - (b) Diabetes
   - (c) Hypertension
   - (d) Nephritis
   - (e) Other
8. *Miscellaneous*
9. *Unknown*

It would be desirable to use the International Statistical Code or some universally recognized code for this classification. However, the above has been used because of its simplicity and, for the purpose of the Alberta study, it has been fairly satisfactory.

Rating of responsibility.—After the cause of death has been discovered the committee tries to decide whether the death was the responsibility of the obstetric or the pædiatric care; whether it was preventable or not; and where the responsibility factors lay. These data are recorded by using a modification of the code used by Kendal and Rose of Philadelphia[2] (Table III).

TABLE III.—RESPONSIBILITY CODE

A. Obstetric	1. Inadequate prenatal care
B. Pædiatric	2. Family at fault
C. Combined	3. Physician, error in judgment
	4. Physician, error in technique
	5. Intercurrent disease
I. Preventable	6. Unavoidable
II. Nonpreventable	7. Unclassifiable
III. Unclassifiable	8. Hospital responsibility

"Hospital responsibility" has been added to cover factors over which the physician has no direct control, and to recognize the hospital responsibility in such matters as inadequate nursing care and inadequate or faulty equipment.

The committee's final appraisal of each death is sent to the attending physician by letter,* with a comment on the case where indicated. This letter is shown below.

NOTICE SENT TO DOCTOR REGARDING PERINATAL DEATH

Dear Doctor:

The following is the classification on Baby.....

born.....CAUSE OF DEATH.....CODE.....

A. OBSTETRIC	1. Inadequate prenatal care
B. PÆDIATRIC	2. Family at fault
C. COMBINED	3. Physician–error in judgment
	4. Physician–error in technique
	5. Intercurrent disease
I. Preventable	6. Unavoidable
II. Nonpreventable	7. Unclassifiable
III. Unclassifiable	8. Hospital responsibility

This classification has been arrived at after consideration of the information that was available to the Perinatal Mortality Committee. Should you have information in regard to this case which may not be known to us, and which might alter the classification, please communicate with us.

Yours sincerely,

At the end of the year statistics are compiled from the information gathered from the province. A letter is then sent to each hospital informing it of its perinatal death rate, and the reliability of that rate for the hospital. Each hospital is also informed of the over-all provincial perinatal death rate and of the average perinatal death rate for hospitals of its own size.

TABLE IV.—ALBERTA PERINATAL RATES 1955–56

Hospital size	*Total births 1956*	*Perinatal death rates per 1000 total births*	
		1955	*1956*
Over 300 beds.....	17,787	23.9	22.0
100 to 299 beds	3035	21.0	20.1
30 to 99 beds.....	9430	22.3	26.9
Under 30 beds.....	4001	23.2	22.7
Indian hospitals....	454	32.3	41.9
Rates for province..		23.9	23.9

*This form was adopted from one used by the University of Manitoba.

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Distribution of perinatal mortality.—Table IV shows the perinatal death rates per 1000 total births for Alberta for 1955 and 1956 according to hospital size.

It will be noted that the provincial rate for the two years is the same. The first two hospital groups, which are the hospitals with their own local committees, have a slightly improved rate for 1956. However, these differences are not significant. Table V shows the breakdown of this 23.9 perinatal mortality rate in 1956.

TABLE V.—PERINATAL MORTALITY IN MATURE AND PREMATURE INFANTS

	Mature	*Premature*	*Total*
Total births	33,282	2034	35,316
Stillbirths	216	204	420
Infant deaths	154	270	424
Total	370	474	844
Death rate per thousand for their own groups	11.1	233.0	23.9

Perinatal mortality rate in prematures.—It will be noted that there are over 100 more deaths in premature infants than in mature ones and that the perinatal mortality for mature babies is 11.1 per 1000 mature births, whereas the same rate for premature babies is 233—21 times as high. It is obvious that prematurity is a major problem from both the obstetric and pædiatric standpoints.

This picture is more graphically shown in Fig. 1.

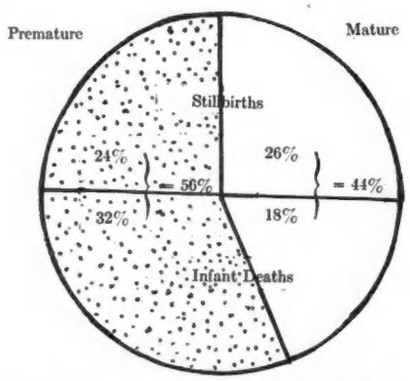

Fig. 1.—Alberta Perinatal Deaths—1956

One of the major problems, then, is in respect to prematurity. A premature infant in Alberta is an infant born weighing 5½ lb. or less. Table VI shows the premature birth rate for the province in 1956.

The prematurity rate of 5.9 is a little lower than the usual rate of 6 to 7%. This is partly due to the fact that stillbirths under 28 weeks' gestation are not included in this figure. The incidence of prematurity apparently decreases as the size of the hospital (and therefore the community) decreases. The difference in the incidence of prematurity between the hospitals of over 100 beds and those under 100 beds is highly significant; the "Z" value, or the standard normal variate, is

TABLE VI.—PREMATURE BIRTHS EXPRESSED AS PERCENTAGE OF TOTAL BIRTHS

Hospitals over 300 beds	$\frac{1256}{17787} = 7.1\%$
Hospitals 100–299 beds	$\frac{188}{3035} = 6.2\%$
Hospitals 30–99 beds	$\frac{415}{9430} = 4.4\%$
Hospitals less than 30 beds	$\frac{165}{4001} = 4.1\%$
Average for above groups	$\frac{2024}{34253} = 5.9\%$

10. The reason for this significant difference is obscure, but no doubt worth investigating.

Table VII reveals a difference in the perinatal mortality rates for premature infants in the different hospital size groups.

TABLE VII.—PREMATURE DEATH RATES PER 1000 PREMATURE BIRTHS

	Still-births	*Infant deaths*	*Total*
Hospitals over 100 beds	84	99	183
Hospitals under 100 beds	123	210	333
Provincial rate	100	133	233

Here again there is a highly significant difference in the perinatal mortality rates between the hospitals of over 100 beds and those under 100 beds. The "Z" value here is 7.21. It is possible that this difference reflects the less specialized equipment and nursing personnel in these smaller centres.

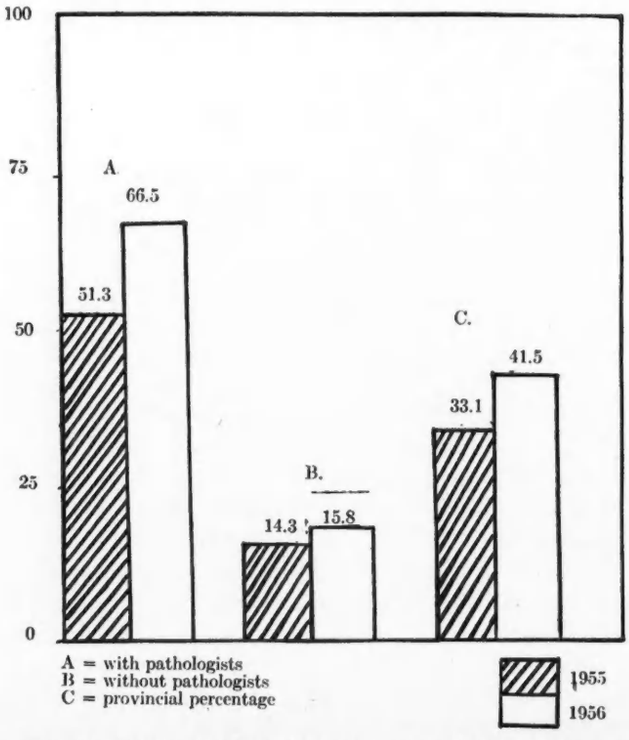

Fig. 2.—Percentages of autopsies on perinatal deaths in 1955-1956.

Autopsy rates.—The autopsy rates for 1955-1956, as shown in Fig. 2, indicate that there has been an increased interest in, and concern about, these deaths.

The Alberta Perinatal Mortality Committee has now been functioning for two and a half years. Although the death rate has not decreased, a major interest has been created in this group of deaths. The co-operation of the medical profession has been very encouraging. As far as the Perinatal Mortality Committee is aware, the medical profession in Alberta would like to see the study continue. The aim of the committee has been to encourage the adoption of recognized standards of obstetric and pædiatric care throughout Alberta. The committee believes that the continuation of this study will inevitably lead to an improved perinatal mortality rate.

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RÉSUMÉ

Les recherches dans le domaine de la mortalité infantile sont intimement liées aux données anatomopathologiques que fournit l'autopsie des enfants morts. L'étude d'un tel problème dans la province d'Alberta se heurte à la difficulté que crée le petit nombre de pathologistes dans cette région du pays. En effet sur plus de 100 hôpitaux dans toute la province, seulement les huit plus grands possèdent un service d'anatomopathologie. Environ 53% des infants qui meurent au cours de la première année succombent dans la semaine qui suit la naissance. Les cas référés au comité sur la mortalité néo-natale et infantile de la province d'Alberta sont documentés à l'aide d'un questionnaire que l'on envoie au médecin traitant. Dans les cas où il y a eu autopsie, la cause du décès est enregistrée d'après une modification de la classification du Dr Edith Potter. Après étude du cas, le comité de l'hôpital ou du district rural, selon le lieu, cherche à établir la responsabilité, et à déterminer les moyens qui auraient pu prévenir le décès. Les résultats sont formulés d'après le code modifié de Kendall et Rose. Le médecin intéressé en est informé par lettre et la compilation des statistiques est envoyée aux hôpitaux. Au cours des deux années qui se sont écoulées depuis la fondation du comité, le taux de mortalité néonatale en Alberta s'est maintenu à 23.9 par année. Il est à remarquer que le taux de mortalité des prématurés (dont le poids à la naissance est inférieur à 2500 g.) est 21 fois plus élevé que celui des enfants nés à terme, ou de poids normal. En dépit de la situation décrite plus haut, le taux des autopsies augmente graduellement. Les résultats obtenus jusqu'à présent, bien que modestes, semblent néanmoins encourageants.

Case Reports

REPORT OF LEUKÆMIA OCCURRING IN FATHER AND DAUGHTER

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HISTORY AND INTRODUCTION

CASES OF A DISEASE which was probably leukæmia were reported in the early 19th century. The blood was noticed to be pale, and this finding was shown by Alexandre Donné to be due to the presence of a large number of leukocytes. At this period it was considered that the leukocyte was the precursor of the erythrocyte, and the disease was thought to be due to a disturbance of this process. The first post-mortem descriptions of leukæmia were published by Rudolf Virchow in 1845,[1] and also by Bennett and Craigie[2] in the same year. It was Virchow who divided the disease into its two main types—"splenic" (myeloid) and lymphatic. In 1846 Fuller diagnosed a case during life, and 15 years later, in 1861, Biermer[3] published an account of two cases occurring in the same family. This remains of historical interest as being the first report of familial leukæmia, although his diagnosis is now considered to have been wrong.[4] It was not until 1922 that the first definite report of familial leukæmia was published by McGavran.[5]

Since then many more examples have been published and reviews have been made. Petri[6] published 11 observations of familial leukæmia. Four of these were rejected by Videbaek,[4] who produced an excellent review in 1947. He rejected many other published cases, and added 13 cases of his own. Altogether he found 82 authentic cases of leukæmia belonging to 37 different families. Since then Carter[7] states that 28 unquestionable cases in 12 different families have been reported. To these can be added the cases reported by Cooke (1953),[8] Steinberg, Farber and Downing (1953),[9] Anderson and Hermann (1955),[10] and Johnson and Peters (1957).[11]

The cases reported here are of a father and daughter. The daughter developed chronic monocytic leukæmia and died on March 19, 1952. The father was found to be suffering from chronic lymphatic leukæmia in September 1956, and is still alive.

CASE 1.—Mrs. E.H., a married woman aged 43, was seen in March 1951, complaining of palpitations, dyspnœa and swelling of the ankles. An appendectomy had been done when she was seven years old, and a fibroadenoma had been removed from the right breast when she was 42. She had had three normal pregnancies and deliveries. The family history was non-contributory.

Physical examination was negative apart from the presence of palpable lymph nodes in the right submandibular region, and marked pallor of the skin and mucous membranes. Her Hb. value was 33%, and

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the erythrocyte sedimentation rate (E.S.R.) was 122 mm. in one hour. The total white cell count was 4800 with 46% immature monocytes, 45% lymphocytes, 8% neutrophils and 1% blast cells. A cell count of the sternal marrow was diagnostic of monocytic leukæmia, with 45% of immature monocytes and 15% monoblasts.

Six bottles of blood were given, and this increased her hæmoglobin to 82%. After one more blood transfusion she was allowed to return home. Whenever her hæmoglobin reached 70-75% she was given a transfusion of blood at home. She received altogether 40 bottles of blood at home and 20 in hospital during the course of one year.

Her white cell count remained steady until October 1951, when it began to rise, and by November 8 it had reached 60,000. She was then given x-ray therapy, and by November 15, the white cell count had fallen to 15,000. In March 1952, she was admitted to hospital again because of severe abdominal pain and menorrhagia. Her temperature was 100° F. and pulse rate 120. There were purpuric spots on the soft palate and tonsillar fossæ. The gums were hypertrophied and purple in colour. There was an area of purpura on the left thigh above the knee. A firm mass was palpable in the abdomen, arising out of the pelvis and reaching halfway to the umbilicus. Her leukocyte count was now 159,200 with 66% monocytes, 11% promonocytes, 6% lymphocytes, 12% blast cells and 5% neutrophils. She was treated with blood transfusions and antibiotics but remained febrile. She became gradually weaker, and on March 19 she lost consciousness and died 2½ hours later.

POSTMORTEM EXAMINATION

Cranial cavity.—The brain was congested and soft. There were petechiæ up to 0.2 cm. in diameter scattered in the cerebral hemispheres.

Thoracic cavity.—Petechiæ up to 0.3 cm. in diameter were scattered under the visceral pleura and on the inner aspects of the thoracic cage. There were multiple subepicardial hæmorrhages up to 0.8 cm. in diameter. There was an excessive amount of dark yellow pericardial fluid. There were no enlarged mediastinal lymph nodes.

Abdominal cavity.—A walled-off hæmorrhagic mass in the right adnexa measured 10 x 8 x 6 cm. and lay in the right iliac fossa. The hæmorrhage had occurred into an ovarian cyst and trekked up into the broad ligament. The liver weighed 2600 g. and was intensely congested. The spleen weighed 740 g. and was firm and congested. The mesenteric and periaortic lymph nodes were soft and enlarged up to 2 cm. in diameter. The adrenals were soft and hæmorrhagic.

Microscopy.—The vessels of the brain, myocardium and pancreas were filled with mononuclear cells. These cells were also present under the endocardium and in consolidated areas in both lungs. The normal architecture of the spleen had disappeared and this organ and the liver were infiltrated with mononuclear cells. The lymph nodes from the mesentery, omentum and periaortic regions showed almost complete replacement by mononuclear cells.

Diagnosis.—Monocytic leukæmia with hæmorrhage into right adnexa.

CASE 2.—Mr. W.M., 79 years of age, is the father of the first patient reported. He was seen in September 1956, when he complained of shortness of breath which had been increasing in the past month, and came on after he had climbed 10 steps. He had also noticed swelling of both ankles for two weeks and loss of 20 lb. in weight over the past few months.

In 1943 he developed tic douloureux which was treated by injections and finally by section of the sensory root of the fifth cranial nerve.

In appearance he was a very thin old man. Small discrete lymph nodes were palpable in the cervical chains, both axillæ, both groins and the right supraclavicular region. Both epitrochlear lymph nodes were palpable. The spleen was enlarged to 14 cm. below the left costal margin and reached below the umbilicus. The liver was felt 4 cm. below the right costal margin. There was pitting œdema of both ankles two-thirds of the way up the legs. The blood pressure was 164/90 mm. Hg and the pulse was regular. Chest movements were poor and mainly antero-posterior. There was anæsthesia in the distribution of the right maxillary nerve. The white cell count was 250,000, with 92% mature lymphocytes, 4% prolymphocytes and 4% neutrophils. The hæmoglobin value was 62% and the E.S.R. 20 mm. in one hour.

He received radiotherapy on 18 occasions in 29 days with no effect on his white cell count. At the end of the treatment the total count was still 218,000. CB 1348 was started on October 15, 1956, in a dose of 10 mg. daily. On November 6, the white cell count was 119,600 and as it was dropping the CB 1348 was reduced to 6 mg. daily. By December 21, the white cell count was 38,500.

On returning home he had recurrent bouts of fever during which he became disorientated. His temperature would rise to 101° F. and on one occasion he had a rigor. In January he was readmitted to hospital in mild congestive cardiac failure. Investigations were as follows: total white cell count 28,000, with 82% lymphocytes, 3% prolymphocytes, 2% monocytes and 13% neutrophils; platelets 136,500, blood urea nitrogen 21 mg. %; total proteins 5.7 g. %, with 3.1 g. albumin and 2.6 g. globulin. The electrocardiogram showed anterolateral myocardial damage, but a transaminase estimation gave a value of 17 units and it was concluded that this was an old lesion. On routine treatment he improved and was discharged home to continue to take 2 mg. of CB 1348 daily.

DISCUSSION

It is usually stated that the occurrence of more than one case of leukæmia in a family is rare, although the evidence about this is conflicting. Guasch[12] conducted a canvass of hæmatologists in all parts of the world. In over 8500 cases of leukæmia there were 39 instances of familial leukæmia. This is an incidence of 4.5%. Videbaek[4] found that in the families of 209 patients with all types of leukæmia 8.1% contained other members with the disease.

The question arises whether more than one case occurs in a family because of an inherited predisposition to develop the disease. This possibility must be carefully considered in view of the growing number of familial cases reported in the literature.

Ardashnikov[14] in a study of 33 pedigrees reached the conclusion that in some cases at least a here-

ditary factor plays a role in the etiology of leukæmia in man. He thought that it was probably a conditionally dominant gene with very low penetrance. This view is supported by Gates,[15] and also by Videbaek. The latter considered it probable that the disease was inherited by irregular dominance.

Videbaek's paper is an important one and he gives figures on the incidence of the various forms of the disease. It has been stated that the familial form of the disease is most often lymphatic, whereas the common form of the disease in the population at large is myeloid. Videbaek disagrees with this view. He has worked out the incidence of the various forms of leukæmia admitted to Copenhagen hospitals in a period of ten years, and finds that chronic lymphatic leukæmia predominates and agrees closely with the incidence of familial forms of the disease. His figures for leukæmia in general are as follows: 41%—chronic lymphatic, 20%—chronic myelogenous, 33%—acute leukæmia, 6% monocytic. Bethell[16] found that in a group of 495 patients the incidence was: 48.3% granulocytic, 43.6% lymphocytic, 8.1% monocytic. In most of Videbaek's families more than one form of the disease was found. He therefore drew the interesting conclusion that the gene was not specific for the type of leukæmia, but was a common leukæmic gene.

One of the main difficulties lies in the interpretation and statistical analysis of the available material. Videbaek for example states in support of a hereditary factor that the onset of the disease in familial cases is at an earlier age than in leukæmia in general. Busk[17] considers this can be explained by the fact that the older patients are unable to give satisfactory information about their ancestors and are underrepresented in the familial groups.

As in other problems of this nature, it is interesting to study the occurrence of the disease in identical twins. In Guasch's[12] survey eight families were reported in which the disease occurred in twins. The four families, however, which had only one twin affected had not been previously reported. It is discrepancies of this kind that make reviews of the literature difficult to interpret.

Some of the most important evidence that a genetic factor is involved lies in the four reports of the disease occurring in three or more members of the same family (Weiss (1927),[18] Steinberg, Farber and Downing (1953),[9] Anderson (1951),[13] and Johnson and Peters (1957)[11]). It is of great interest that in two of these families the parents were consanguineous.

It is impossible to reach any definite conclusion about the genetic factor in leukæmia from the evidence currently available. Some authorities consider that no genetic factor is involved and that the occurrence of more than one case in a family is due to chance. Against this, however, must be weighed the evidence collected by Ardashnikov and Videbaek.

The uncertainty about the inheritance of leukæmia is largely due to the fact that, in diseases which involve genes with low penetrance, other factors both hereditary and environmental will modify the point at which the disease appears, and also the disease itself. Of the environmental factors, infections and irradiation have long been considered to be implicated. In fact, leukæmia is still considered by some authorities to be an infection. Kellett,[19] for example, carried out an interesting investigation. He reports the occurrence of acute myelogenous leukæmia in one of identical twins. In the same paper he also made an analysis of the 63 cases admitted to hospital over a four-year period. Eight came from the same area as his reported case and the rest occurred sporadically. Five of the eight occurred under "almost epidemic conditions". He postulated that the disease was an infection, but of low infectivity due to the intervention of some secondary factor such as an insect vector.

The most damaging evidence against the theory that the disease is purely an infection is the fact that it has never been reported in husband and wife (Ardashnikov). Furthermore, in the cases reported here and in many other familial cases, the time interval is too long to make an infectious etiology likely.

X-rays have been shown to cause leukæmia (Simpson *et al.*,[20] Folley *et al.*[21]). The most interesting recent information on this aspect of the subject is a preliminary report published in 1956 by Stewart[22] on the effect of diagnostic irradiation *in utero*. It was found that 42 of the children who died from leukæmia had been x-rayed *in utero* as opposed to 24 of a control group and that 43 children who died from "malignant diseases" had received similar irradiation compared with 21 of a control group. In Simpson's paper the control group was not very satisfactory but this objection cannot be made about Stewart's report. This was a preliminary report of a survey which at that time had covered 547 cases and controls. The returns for over 1300 cases and controls are now available[23] and the findings of the preliminary report are confirmed. It is of interest in this connection to note that nearly all twins are submitted to diagnostic irradiation *in utero*.

It is probable that even small doses of radiation can cause leukæmia and that there is no threshold dose below which it is safe. In fact, in a recent article, Lewis[24] has shown that the dose of radiation bears a linear relationship to the occurrence of leukæmia. He suggests that the explanation may lie in a somatic gene mutation which has been induced by the radiation. He also points out that cases of radiation-induced leukæmia will tend to obscure the analysis of the hereditary component.

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SUMMARY

Leukæmia of different cell type occurring in a father and daughter is reported. Comments are made on the genetic aspects of the disease.

The author would like to thank Dr. J. M. Kilgour for his helpful comments and advice, and also Dr. R. E. Beamish and Dr. W. H. Ostapovitch for permission to publish the report of the first case.

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REPORT OF A FATAL CASE OF LISTERIOSIS MENINGITIS IN A SEVEN-DAY-OLD INFANT

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LISTERIA MONOCYTOGENES was first isolated by Murray, Webb and Swann[1] in 1924 from infected laboratory rabbits. The organism has since been isolated from 27 species of animals and possesses a fairly universal distribution, being reported from 26 countries in five continents (Murray[2]). Cases of human listeriosis are cosmopolitan in distribution but rather rare.

Human listeriosis was first recognized in Canada in 1951 when Stoot (as reported by Reed *et al.*[3] and Johnston *et al.*[4]) isolated *Listeria monocytogenes* from an infant with fatal meningitis. While recently reporting three cases of human listeriosis Reed *et al.*[3] suggest that the occurrence of 15 cases in Canada since 1951 may indicate either increasing incidence of such infections or an increasing awareness of them by bacteriologists.

Listeriosis first attracted attention in Newfoundland early in 1955 when, in an epidemic of distemper among dogs in Labrador, *Listeria monocytogenes* was isolated from two of the dead animals forwarded to the Animal Diseases Research Institute, Hull, Que.

In November 1956, a 7-day-old female infant was admitted to the Isolation Unit of the General Hospital in St. John's with symptoms of meningitis, gastroenteritis, and a respiratory infection. The child, who was seriously ill, had been previously brought by the mother to the office of a pædiatrician, who immediately referred the infant to hospital. The mother stated that for the previous 24 hours the child had been feverish, dyspnœic and anorexic, and had been having loose green stools. The obstetrical history was negative. The baby had been born at term and the delivery, which was normal, was done in the home by a midwife. Birth weight was 8 lb. 8 oz. There were eight siblings, all alive and well.

On initial examination in hospital, the infant was desperately ill and almost moribund; she weighed 7 lb. 4 oz., and was in apparent respiratory distress. Temperature was 101°F. There was slight cyanosis of the lips. Respirations were rapid, and crepitant rales were heard at the left lung apex. Abdominal examination was negative. The anterior fontanelle was bulging, but there was no neck rigidity and the Brudzinski and Kernig signs were negative.

Lumbar puncture was performed. The C.S.F. was not under pressure but appeared turbid; its white cell count was 5950, with 98% neutrophils and 2% lymphocytes: total protein was 500 mg. per 100 ml.

Direct examination of a Gram-stained smear of the centrifuged sediment of the C.S.F. revealed the presence of many red and white cells (polymorphonuclear cells predominating) and a moderate number of Gram-positive diphtheroid-like bacilli without metachromasia, some of which were intracellular.

The admission clinical diagnosis was acute meningitis, probably influenzal or pneumococcal. The possibility of the diphtheroid-like organism found in direct smears of the C.S.F. sediment being a contaminant was considered, but because the spinal fluid was freshly examined and because these organisms were present in moderate numbers, often phagocytized, they had to be regarded bacteriologically as the etiological agent.

Treatment with adequate dosage of intrathecal and intramuscular crystalline sodium penicillin (5000 units intrathecally; intramuscularly 1 million units immediately and ½ million units 3-hourly) was instituted and supplemented by sulfadiazine, chloramphenicol and streptomycin; the child was also placed in an oxygen tent.

About an hour after admission, vomiting started with generalized convulsions and expectoration of copious amounts of green mucus. Despite the antibiotics, supportive fluids, oxygen, and suctioning, the child died 15 hours after admission.

AUTOPSY REPORT

GROSS DESCRIPTION

General: The body was refrigerated until autopsy 12 hours after death. The lips and gums were slightly cyanotic, and there was blood-streaked frothy white mucus in the mouth and nasal cavities, with some discharge of this material from the nose. The abdomen was protuberant. There were no other external features of note.

Neck Organs: The larynx, pharynx, and trachea contained reddish, frothy mucus, and the lining mucosa

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of the entire upper respiratory tract was quite injected. The thyroid and thymus glands were not remarkable.

Thoracic Cavity: There was approximately 50 ml. of watery-green fluid in each pleural cavity. The lungs were about three-quarters expanded and their serosal surface was purple in colour, except for the anterior borders of the upper lobes which were speckled, greyish-yellow, pillowy and apparently aerated. Apart from the latter areas, all lobes of both lungs were firm on palpation, and on cut section revealed a markedly œdematous, congested, and apparently diffusely consolidated cut surface. All the bronchi exuded a considerable amount of frothy reddish fluid, and the lining mucosa was markedly injected.

The pericardial sac, the pericardial fluid and the heart were not remarkable. The heart valves were normal, and the myocardium was firm and reddish-brown.

Abdominal Cavity: There was no free fluid in the peritoneal cavity. All the organs were in proper position and clothed by smooth, glistening serosa. The stomach and small intestine were markedly distended but the large bowel was normal. When the stomach was opened, approximately 100 ml. of clotted blood was found. There was a large mucosal ulcer measuring 2 cm. in diameter, situated on the posterior wall of the fundus near the greater curvature. Distributed irregularly around the periphery of this large ulcer were several smaller pinhead-size mucosal ulcers. In the duodenum and in several loops of the upper jejunum, dark brown material like altered blood was found in the lumen, but there were no areas of mucosal ulceration, and it was presumed that this material had passed down through from the stomach.

The liver weighed 175 grams and had a smooth brownish-red capsule. The cut surface of the liver was uniformly congested, pale brown, with scattered tiny yellowish areas. The spleen and pancreas were not remarkable. Both adrenals were large, and on cut section the medulla in both organs showed a small recent hæmorrhage. The kidneys, ureters, and urinary bladder were essentially normal. The uterus and adnexæ were not remarkable.

Cranial Cavity: A diffuse greenish purulent exudate was distributed over the entire brain, but was more prominent and heavier over the base, where it extended downwards around the medulla and the cord. The brain weighed 420 grams and showed generalized congestion. In some areas the exudate on the surface was so heavy as to obscure the vessels and exiting cranial nerves. Slicing the brain revealed nothing of note apart from congestion of blood vessels. The cranial venous sinuses contained fluid blood only, and the middle ears and mastoids were normal.

MICROSCOPIC DESCRIPTION

Lungs: Sections of the lung revealed a confluent hæmorrhagic bronchopneumonia. All the bronchioles and alveoli were engorged with œdema fluid containing red blood cells, a small amount of fibrin, and a paucity of inflammatory cells. The latter were chiefly of the mononuclear type, consisting of lymphocytes, monocytes and macrophages. The bronchial and bronchiolar mucosa throughout was quite congested, and there was moderate lymphocytic and monocytic infiltration of their wall.

Stomach: Sections of the stomach revealed a large area of acute ulceration involving mucosa, muscularis mucosa and submucosa. The base was infiltrated with equal numbers of monocytes and neutrophils.

Liver: The sections of liver showed marked chronic passive congestion and there was a moderate degree of diffuse extramedullary hæmatopoiesis. A very occasional tiny focal area of necrosis was seen, in and around which occasional monocytes and very occasional eosinophils were found. There were also occasional portal triads showing pericholangiolitic infiltrations of monocytes and eosinophils.

Adrenals: Sections of the adrenals revealed a moderate degree of fresh hæmorrhage into the medulla. The cortical zone showed slight hyperplasia of the mid-zone but otherwise it was not remarkable.

Brain: Microscopically, the arachnoid meninges showed marked infiltrations of polymorphonuclear leukocytes and there were also moderate numbers of lymphocytes and monocytes intermingled in the inflammatory exudate. In both the cerebral cortex and the cerebellum quite a number of the capillaries showed slight perivascular cuffing of lymphocytes and monocytes. The sections of the brain were stained especially for bacteria by the Gram-Glynn method, and these showed moderate numbers of Gram-positive bacilli morphologically similar to the *Listeria monocytogenes* isolated bacteriologically from the spinal fluid.

Anatomical Diagnoses

1. Acute cerebrospinal meningitis; purulent; *Listeria monocytogenes.*
2. Acute bronchopneumonia: bilateral confluent; all lobes.
3. Multiple acute gastric ulcers with hæmorrhage.
4. Hæmorrhage into adrenal medulla; minimal; bilateral.
5. Early acute focal necrosis of liver; minimal.

BACTERIOLOGY

Cerebrospinal fluid when collected before the death of the infant was seeded on various media which included blood agar and infusion broth. A heavy growth of discrete pinhead-size greyish colonies was obtained on blood agar which when smeared and stained appeared to be Gram-positive bacilli with morphological characteristics of a diphtheroid. Growth in the infusion broth revealed the same type of organism. In the subsequent identification of the strain, *Listeria monocytogenes* amongst other organisms had to be considered.

At the necropsy, swabs were made from pleural cavity, lungs, and pus from meninges. Blood from the heart was collected aseptically for culture. The same organism as previously isolated from the cerebrospinal fluid was grown from the pus of the meninges. No isolations were made from the pleural cavity swabs, the lung swabs or the blood culture, and these were bacteriologically sterile at 37°C.

Various cultural and biochemical methods were employed in the identification of the isolated strain. Inoculation into two rabbits gave the following findings: The first rabbit was given 0.1 ml. of a broth culture intradermally. The animal appeared normal when autopsy was performed two days later, even though the organism was re-isolated from the site of injection. Blood cultures and cultures of liver swabs were sterile after 72 hours' incubation of the latter and one week for the former. Smears of rabbit's blood prior to injection and again at autopsy showed monocytes to be 4% and 20% respectively. A moderate

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number of nucleated red cells were present in the second smear.

The second rabbit was given 0.5 ml. of broth culture intravenously. This rabbit died and was autopsied two days later. The organism was isolated from liver swabs and from blood culture. A comparison of the differential white cell counts in peripheral blood smears made prior to injection and at autopsy showed an increase in monocytes from 4% to 35%. The smear made from this rabbit at autopsy also showed a moderate number of nucleated red cells.

The organism itself was a Gram-positive, non-spore-forming bacillus averaging 0.5 x 2.0 microns. Slightly curved forms were common. Sluggish motility was demonstrated only on cultures grown at room temperature and in those cultured in the refrigerator at 5°-7°C. The results of the biochemical tests as well as the odour of cultures were in perfect agreement with the characteristics listed for *Listeria monocytogenes* in Bergey's *Manual*. The marked increase in monocytes after injection into rabbits is quite diagnostic, since this characteristic is exhibited by strains of *Listeria monocytogenes* derived from all sources.

On primary isolation the strain was non-hæmolytic on human-blood agar plates, but showed a narrow zone of beta hæmolysis on rabbit-blood agar plates. The strain isolated was sensitive to penicillin, aureomycin, terramycin, erythromycin, chloramphenicol and streptomycin.

SUMMARY

A case of fatal meningitis in a 7-day-old infant is reported in which the causal agent was identified as *Listeria monocytogenes*. Occurring rarely throughout Canada and the United States, this is the first record of human listeriosis in the province of Newfoundland. This case is also of unusual interest because of the age of the patient.

An attempt was made by Dr. J. W. Davies, Acting Chief Medical Health Officer of the Newfoundland Department of Health, to establish a source of infection. The home surroundings were poor and somewhat unhygienic. A cat was kept around the house but specimens from this animal and from two mice trapped on the premises failed to grow this organism bacteriologically. In any case, there was no history or clinical evidence of the infant having been bitten or scratched. An effort was made by Dr. Davies to obtain vaginal swabs or specimens of vaginal secretions from the mother for bacteriological investigation to determine whether the child might have acquired the infection from the birth canal, but the mother was totally uncooperative and refused to allow the specimens to be taken. The midwife has not been examined.

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PRIMARY AMYLOIDOSIS*

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IN 1929 LUBARSCH[1] first described and defined primary amyloidosis as a distinct entity. The criteria which he set forth and which differentiate primary from secondary amyloidosis are the absence of antecedent or co-existent disease, the predominant involvement of mesodermal tissues, variability in staining reactions and a tendency to a nodular deposition of the amyloid.

To date, about 150 cases of primary amyloidosis have been reported. This number would be considerably increased if cases of primary amyloidosis in old age—so-called senile amyloidosis—were included. This latter condition is said to involve the heart in 15% of men and 10% of women over the age of 70. Primary amyloidosis has no sex preponderance. Its peak incidence is between 45 and 60 years. The average survival time is significantly longer in primary than in secondary amyloidosis, although present-day therapy has influenced greatly not only the survival time but also the incidence of secondary amyloidosis. It may well be that in the years to come secondary amyloidosis will become as uncommon as primary amyloidosis, or even rarer. Usually in primary amyloidosis death is due to congestive heart failure or terminal infection.

Recent comprehensive reviews of the literature have been made by Mathews,[2] Symmers[3] and Milliken.[4] For further review of the literature the reader is referred to these excellent articles.

Clinical history.—A 63-year-old white woman was admitted to Victoria Hospital, London, Ont., on October 7, 1955, complaining of difficulty in speaking, a swollen red tongue and a firm swollen neck. The history of the present illness dated from almost five years previously, at which time the patient noted some slight stiffness of her fingers. Since that time she had noticed swelling of her tongue and neck, with progressive difficulty in speaking and swallowing. On several occasions she was admitted to Sarnia General Hospital, where biopsies of cervical lymph nodes and tongue were done. Just prior to admission here she noticed slight swelling of her ankles.

Physical examination.—Physical examination on admission revealed a remarkable appearance suggesting myxœdema at first glance. The tongue and lower lip were swollen, enlarged and almost woody to palpation. Massively enlarged lymph nodes together with brawny œdema were noticed in the neck. Palpation of the back, extremities, and thenar and hypothenar eminences revealed a generalized woody feel.

Laboratory studies.—Laboratory studies revealed albumin 3+ in the urine and a specific gravity of

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1.008. Hæmoglobin value 13.7 g. %; white cell count 7000; sedimentation rate 38 mm. in one hour. Bromsulphalein 2% retention after 45 minutes. Radioactive iodine pick-up was normal. Non-protein nitrogen (N.P.N.) 16 mg. %. Cephalin cholesterol flocculation was negative. Thymol turbidity 4 with a negative flocculation. Plasma protein value was 5.4 g. with an albumin fraction of 3.3 and globulin of 2.6. The A:G ratio was 1.6:1. Serum cholesterol 184 mg. %. A Congo red test showed 73% of the injected dye remaining in the blood at the end of one hour. A barium swallow showed some hesitation in initiating the act of deglutition. The increased size of the tongue resulted in encroachment upon the lumen of the pharynx and made swallowing difficult. The trachea and cervical œsophagus were displaced towards the left side, with some localized narrowing of the trachea immediately inferior to the glottis. A biopsy of the left forearm revealed amyloidosis, and its appearance was consistent with primary amyloidosis.

The patient was discharged in November 1955 and readmitted January 1, 1956, complaining of increased difficulty in swallowing, vomiting and abdominal distress. On January 15, 1956, she developed cerebral thrombosis with a right-sided hemiplegia. She lapsed into coma and died on January 17, 1956.

Autopsy findings.—For the sake of brevity, only positive and significant findings will be given. The body was emaciated. There was no peripheral œdema. The subcutaneous tissue felt doughy to firm and was yellow and indurated.

Selected blocks of tissue were fixed in 10% formalin and Zenker's fixative. Sections were stained with hæmatoxylin and eosin, Mallory's phloxin, Highman's modification of Bennhold's Congo red, crystal violet, iodine, Masson's trichrome, periodic acid-Schiff (PAS), van Gieson's, Rinehart's modification of Hale's dialysed iron, Verhoeff's elastic tissue and Foot's reticulum stain. The heart, tongue, skeletal muscles, subcutaneous fat, œsophagus and gastro-intestinal tract were the sites of the main pathological changes. The heart weighed 282 g. The visceral pericardium was thickened and very indurated. Extremely firm, irregular grey areas were seen in the myocardium in general and in the papillary muscles. The atria and atrial appendages were indurated and leathery. The mitral and tricuspid valves were thickened and rigid, especially towards the free margins of the valves. Amyloid was deposited in the walls of many blood vessels. In the epicardial fat it was deposited in a very patchy nodular distribution on the reticulum and fine collagen fibres of the fibrous tissue and surrounding and between the fat cells. In the myocardium, amyloid was deposited in the interstitial tissue. In the valves it appeared to be related to collagen and elastic fibres deep in the valves rather than to lie under the endothelium.

In the skin and subcutaneous tissues small amounts of amyloid were deposited in small nodules in the corium but the subcutaneous fat was involved extensively in a manner similar to that of the epicardial fat.

The tongue was greatly enlarged, thick, very indurated and pale greyish-yellow. The skeletal muscles had a similar appearance. In the tongue and the muscles abundant amyloid was deposited in the interstitial tissue. In general the sarcolemma was well preserved and uninvolved. In the interstitial tissue amyloid

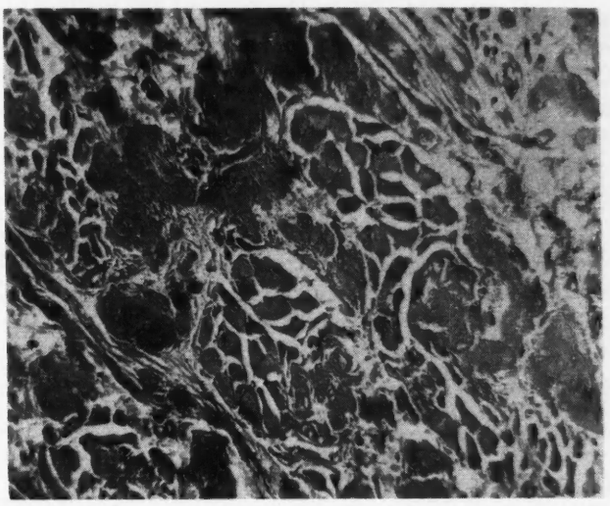

Fig. 1.—Section of tongue. Amyloid deposits causing pressure atrophy of striated muscle. Hæmatoxylin and eosin. ×120.

was deposited in blood vessel walls and on the collagen and reticulum of fibrous tissue and between fat cells.

In the alimentary tract amyloid was deposited in a nodular pattern in the deep submucosa and in the interstitial tissue of the muscularis. In the skin, tongue, vocal cords and gastro-intestinal tract there was a pale subepithelial zone essentially uninvolved with amyloid.

In the parenchymatous organs such as lungs, liver, spleen, kidneys, pancreas, adrenals and thyroid, amyloid was minimal and almost entirely confined to the walls of blood vessels.

Examination of the brain revealed thrombosis of the left internal carotid and anterior cerebral arteries and an infarct in the left frontal lobe.

DISCUSSION

No known pre-existing or associated disease was present in this case.

The distribution of the amyloid deposits was one of the outstanding features. The predominant involvement of mesodermal tissues and minimal involvement of parenchymatous organs is usual in primary amyloidosis. In the mesodermal tissues amyloid was deposited just beneath the endothelium and between muscle cells and elastic fibres

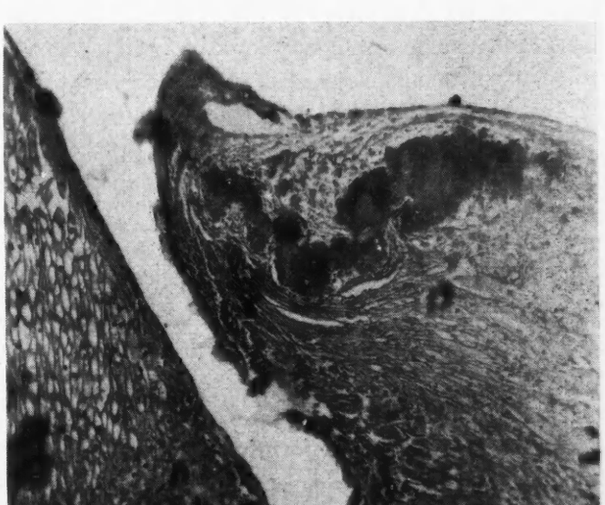

Fig. 2.—Amyloid deposit in papillary muscle of heart. Hæmatoxylin and eosin. ×120.

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of the media of blood vessels, but very often the amyloid deposits were unrelated to blood vessels. This is the intriguing feature of the amyloid deposition in this case. From the examination of many different tissues and the use of different staining techniques, it seems that the amyloid deposits were related intimately to collagen, reticulum and elastic fibres. In blood vessels, heavily involved, the elastic tissue was frayed and fragmented, and had disappeared almost entirely. It is a question whether it had been consumed in some way in the amyloid deposit. With Mallory's phloxin the amyloid stained intensely red, a brighter red than with eosin, and in sharp contrast to other acidophilic tissues such as muscle and collagen. With the Congo red stain the amyloid in this case tinctorially was not significantly different from the amyloid of secondary amyloidosis. However, the negative Congo red test carried out clinically suggests that the amyloid in this case had a feeble affinity for Congo red. Mallory's iodine stain was quite unsatisfactory in the fixed tissue sections of this case. In Masson's trichrome stain the amyloid stained in a closely similar manner to collagen. However, in van Gieson's stain the amyloid stained a faint yellow-brown or khaki colour, in sharp contrast to collagen, which stained red. The amyloid in this case was PAS positive, giving a light to fairly intense red coloration. This is of little differential value, if any, since many substances and structures such as polysaccharides, mucins, collagen, elastic tissue, reticulum and epithelial basement membranes give positive PAS reactions. In the dialysed iron preparations with van Gieson's counterstain a good distinction was seen between collagen (red), mucopolysaccharides (blue) and amyloid (buff, orange to faint greenish-yellow). Thus it is seen that the amyloid in this case fails to stain for mucopolysaccharide. Glycoproteins give a similar staining reaction to that obtained by the amyloid in the dialysed iron preparation. Since chrondroitin sulphuric acid is the precursor substance for mucin, since mucin is a mucopolysaccharide and since amyloid gives a negative reaction for mucopolysaccharides, it is concluded that, along with other histochemical reactions, this information would indicate that amyloid does not contain chrondroitin sulphuric acid and that it probably is a glycoprotein.

The pathogenesis of amyloidosis, and actually the chemical nature of amyloid, are still controversial and much in doubt. Teilum[5] has suggested a possible relationship between amyloidosis and certain collagen disease, for instance, rheumatoid arthritis. Jones and Frazier[6] noted the relationship between amyloid and perimysial reticulum and speculated on a possible metabolic role of reticulum in the transfer of material in one direction or the other.

SUMMARY

A fatal case of primary amyloidosis, diagnosed correctly antemortem and subsequently studied at autopsy, is reported. Clinically, the disease was characterized by insidious onset, long clinical course, enlargement and induration of the tongue, difficulty in speaking and swallowing, woody induration of skeletal muscles and subcutaneous tissues and œdema of the legs. The amyloid was deposited in a nodular manner, chiefly in mesodermal tissues involving especially the heart, skeletal muscles, tongue, subcutaneous tissue and alimentary tract. Its special staining reactions and some of its histochemical characteristics are discussed. Amyloid is believed to be a glycoprotein, but its nature and the pathogenesis of amyloidosis are still controversial and uncertain. The possible relationship of amyloid to collagen, elastic tissue and reticulum is mentioned.

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Special Article

THE CHANGING PATTERNS OF WORK SATISFACTION*

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INTRODUCTION

THE MORES of our present industrial society are such that to be at work is the accepted pattern of social behaviour; not to be at work is the abnormal. The labourer who wins a fortune in a sweepstake, rarely, if ever, gives up the idea of working.[1] The millionaire's son, more often than not, feels compelled to follow his father's example and toil to keep the family coffers replenished. Yet, in spite of these group and individual characteristics, it is apparent that it takes but little to make large segments of our wage-earning population exhibit gross social abnormality by not going to work.

To elucidate the etiology and social pathology[2] of this manifestation of psychosocial disease[3] is probably not possible with the means available to us today. It is therefore necessary to adopt, for the present, the time-honoured method of recording the natural history of the disease, and by this gain some inkling of the processes at work in the problem under review. The natural history of work satisfaction will therefore be outlined, so that we may understand more readily today's symptoms of work dissatisfaction and perhaps suggest a therapy.

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PRIMITIVE SOCIETY

Compared with the complex sociological structure we euphemistically label "modern western civilization", there is something refreshingly understandable about the mores of those we deprecatingly designate as belonging to a "primitive society". Such a primitive society is characterized by its feeling of kinship and cohesion and also by the absence from its vocabulary of any word or symbol corresponding to modern man's concept of "work". This state of affairs is easily explainable when it is remembered that in such a society building a hut, exchanging goods, hunting and fishing, raising a family or attending a religious ritual, are not tasks but facets of what for a better term can be called "total living".

A male child born into such a close-knit, well-integrated group does not have the doubts, fears, anxieties and frustrations of his more civilized counterpart. Unlike the youth of our own society, he grows up with an eager anticipation to play his part in the life of the community. This impatience is cleverly whetted, and at times assuaged, by suitably spaced rituals which, by their symbolism, allow him to feel an ever-increasing integration into the life of the tribe. Eventually he will end up as a fully fledged and, even more important, a fully accepted member of the tribe – i.e. he becomes a "worker", to use modern terminology.

This sense of "belonging" buffers the adult male from the emotional upsets produced by sickness, accident or the loss of a loved one. Our "primitive" savage does not suffer, as does our modern industrial worker, from feelings of not belonging, loneliness, and rejection.

MEDIÆVAL SOCIETY

The next fairly well-defined era is the mediæval. The beginning of this era was characterized by the settling down of the hitherto nomadic merchants in the new towns. This was the result of two major trends – first, the disintegration of established empires accompanied by the disruption of the old trade routes; second, the decay of the feudal system.

In feudal times the population was made up of many small discrete human hierarchies with the noble lord in his castle at its head, his position made secure not only by the geographical location and architectural subtleties of his abode, but also by the presence of armed retainers. The unfree serfs were tightly bound to their lord's land, but as recompense they did have feelings of security because of these armed retainers.

Social life in these times was centred round the manorial village. But as the power of the nobles waned and the merchants lost their wanderlust, new towns began to develop with merchants as a new class. Naturally the nobles resented the settling of these newcomers who were neither peasant nor blue-blood, but with an adaptability that was not entirely altruistic they accepted the merchants as a social group.

This radical social change did not come about without some antagonism on the part of the land-owning nobles towards the merchants. To protect their new-found liberties, the merchants banded together in merchant guilds. The serfs in this new social setting developed into artisans and craftsmen. Industry began to flourish. The craftsmen in their turn formed craft guilds to protect their interests from the economic tyranny of the merchants. The guilds encouraged high-quality workmanship, demanded fair prices, and developed the apprentice-journeyman type of training. The master craftsman was his own master, his hours of work were of his own making, he obtained personal satisfaction through pride in his own accomplishment, his financial rewards were to the mutual satisfaction of himself and the purchaser, and his status in society was clearly defined.

These social changes also brought about changes of deeper sociological significance. Human society was beginning to stratify into social classes. It might sound somewhat reactionary to say that this new class distinction was by no means a bad thing. The acceptance of the stratum into which a man is born prevents the development of many of the emotional ills that plague us today. In such a society each man is respected for what he is, and most men strive to be the best in their own particular skill. "A society cannot exist unless it satisfies certain psychological needs as well as the obvious material ones, and amongst the most important of the psychological needs is the need for status and function."[4]

MODERN INDUSTRIAL SOCIETY

This period can be said to date from the days when coal became a fuel and a source of energy, but the real industrial era did not really begin to flourish until the steam engine became a refined and reliable machine. Such a machine permitted the development of modern industry, with a large output of finished goods, but employing by comparison a small number of wage earners.

In theory, this flurry of technological progress made it possible for industry to supply all the basic requirements for an entire population. In theory, it also allowed a mass rise in the standard of living. With these added material advantages and with machines taking over the job of many men, it should have been possible for the average man to find some leisure time in which to enjoy some new-found freedom and act and behave as an independent unit—an individual.

There was evidence from the earliest phases of the industrial era that the individual was indeed being recognized as a human being. This evidence is perhaps most obvious in the cultural fields. Plays which in the early days had characters representing broad types and classes began to characterize individuals, with the personality and psychological make-up of each character outlined. This gradually evolved into expressing through the medium of the play and the players the problem of human relationships.

The novel also showed the influence of this change in thinking and began to emphasize the person as an individual. This trend has continued to the point where today the novel frequently becomes the medium for the author to express his own emotions through the agency of his characters.

Pictorial art followed the same path—from the conventional representation of a religious theme

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to the individual artist's interpretation of people and things around him and finally, in our present day, to the artist's apparently gaining immense individual satisfaction and relief from putting up his own Rorschach for the laity to admire.

Music similarly evolved from the rhythmic tribal beat, through music impressive and feeling because of its religious motif, up to the days when a composition possessed the trade mark of its individual composer and down, perhaps to the present day, when the composer utilizes orchestration for the production of a cacaphony of discord and percussion to release his own hostilities and frustrations.

The technological progress of the industrial era thus allowed the individual to emerge. These increasing opportunities for self-expression and improvement in the standard of living can certainly be entered on the credit side of the industrialization of society.

But unfortunately entries have also to be made on the debit side. The increased output of the industrial plants with the maintenance of bare minimum wages began to result in the disintegration of social justice and a total disregard for the mediæval craftsman's concept of a "just price". Wealth began to accumulate in the hands of a few "rugged individuals". With increasing emphasis now on the individual, and the accumulation of wealth being regarded as an index of success, it was but logical to regard the unsuccessful "without scruple or pity". "A capitalistic economy put the individual entirely on his own feet. What he did, how he did it, whether he succeeded, or whether he failed, was entirely his own affair."[5] The successful looked upon the unfortunate without sense of responsibility, obligation, or even guilt.

Not being devoid of intelligence, the successful "rugged individual" was not at all averse to capitalizing on both scientific theory and religious orthodoxy to justify his attitudes. Darwin's "Origin of Species" with its concept of "survival of the fittest" fitted in beautifully with his social and business attitudes. Protestantism's view that religion was a personal matter between each man and his God, allowed him to attend church service every Sunday with a clear conscience and to thank his God with genuine humility for his material success.

Similarly he could view with equanimity the hovels, the filth and the disease of his employees and explode with righteousness when these less fit began to organize unions. The wealthy Victorian industrialist was not a heartless, aggressive, unfeeling plutocrat; he was living by a philosophy that cleverly combined two seemingly incompatible views of life — the scientific and the religious. He should not be vilified but rather complimented upon the nimbleness and clarity of his thought processes. It must not be forgotten that this Janus of the industrial revolution created modern industry, and his rugged individuality started an industrial chain reaction that has changed the face of the world, for better or worse, more in the past one hundred years than in the previous two millenia.

So much for the changing philosophies and attitudes of the "haves" during the rough-and-tumble days of the birth of the modern industrial complex. But what was happening to the "have nots"? The most obvious and distressing fact was that work had no longer any personal satisfaction, and still less, any social significance to the worker. Yet if the wage earner had lost satisfaction in work *per se*, what alternative had he, if he still wished to derive some satisfaction from living? He was now a city dweller. He no longer was psychologically capable of enjoying the satisfaction gained from tilling the soil. Gone were the old skills. He could no longer find that inner satisfaction granted to those who are real craftsmen. He soon realized that in this new age of the machine he was but a nameless, faceless nonentity tending a machine, a machine that was looked after by its owner with more care and affection than its human attendant. Even more disconcerting to the worker was the obvious fact that the replacement of such a machine was much more difficult and expensive than the replacement of the worker.

Work had become a dismal routine, a time-consuming drudgery, and the only purpose in doing it was to receive a pay-cheque so that he might enjoy those things that made life pleasurable. No wonder morale suffered, output fell, the worker became irresponsible and the quality of work indifferent. These symptoms were but manifestations of the worker's feeling of humiliation and hostility.

Some of the historical origins of some of our present-day problems with labour should by now be apparent. "The industrialist has taught his employees that work is a painful and unpleasant necessity, and he is now distressed that they believe him; he has treated them as machines and is surprised when they behave as such. He asserted that the fear of starvation was the main incentive to work, and now a thoughtless government has removed the fear and incentive by the Welfare State. Vainly the industrialist seeks for other means whereby the workers may be bribed to work — he produces welfare schemes, holidays with pay, dances, outings, free medical care, and so on — some of which are excellent ideas, others merely an insult to the intelligence. In short he satisfies all the possible physical needs and leaves the psychological ones — responsibility, pride of craft, self-respect, status, and sense of social usefulness, still unsatisfied."[4]

FACTORS IN WORK SATISFACTION TODAY

There are perhaps six easily recognizable factors contributing to work satisfaction.[6] Four of these, prestige and status, sense of belonging, approval and creativeness, have already been discussed. The two still remaining, money and security, loom large on the labour-relations horizon these days and perhaps deserve special mention.

MONEY

As indicated earlier, the change from an agricultural to an industrial economy greatly increased the significance of money. Money, of course, should be a means, not an end. The press would have us

believe that all signs and symptoms of labour unrest have as their basic pathology a desire for higher wages. But opinion polls amongst workers do not substantiate this idea. Quality of supervision, degree of recognition of the individual worker, opportunities for satisfactory contacts, all rated higher in the opinion of those polled than the actual wage level. Though the pay package attracts the worker to the plant, he is perhaps even more strongly attracted away from work by values even more potent than those provided by money alone – leisure, hobbies, companionship and sport. In consequence one cannot predict the behaviour of a worker after a wage increase.

The place of work is where the worker hopes to secure his basic satisfactions but seldom does. In consequence he feels dissatisfied and thwarted in an intangible way. Money being regarded as the panacea for most of our ills, the psychologically uneducated worker demands more. He then becomes still more dissatisfied when with the additional money he feels as emotionally unsatisfied as before. Such an attitude on the part of the workers of course starts a spiral of wage increases, in which everybody suffers, and the discontented worker still remains discontented.

SECURITY

The demand for "security" now seems universal. It has loomed large on the labour-relations scene this past year or so with the prominence given to the idea of "guaranteed wage". Union leaders obviously have not read sociological history, nor have they apparently had a basic course in mental health, for what they have failed to understand is that the demand for "security" amongst the rank and file is not synonymous with "economic security".

Everybody feels "insecure" when he does not know what he wants, what is expected of him, or where he really belongs – the lack of security so bitterly complained of is in reality nothing more than an expression of widespread "anxiety". This, in turn, leads to lowered morale, and to mutual ill-feeling on the part of management and labour, and eventually ends up with another cycle of spiralling wage increases. A "guaranteed wage" contract would not appear to be a specific therapeutic agent; it may perhaps provide some short-term symptomatic relief.

CONCLUSIONS

It should be apparent from this brief review that the old "carrot and stick" attitude towards work satisfaction is outdated. It also has to be remembered that workers throughout the ages, and irrespective of their jobs and environment, have always been real *individuals*. Consequently, workers cannot be categorized into groups; they have to be considered as people. Progressive management realizes this and pays as much, if not more, attention to the individual worker as to his inanimate environment. Again, because workers are people, they must be allowed to assert themselves. Management must refrain from being too benevolent, not only on tactical grounds, but on sound psychological ones. It must likewise refrain from trying to anticipate every desire of the worker. By allowing him or his representative to initiate change, the sense of participating or belonging is enhanced.

It must be obvious that the old class struggle has lost a lot of its bitterness and vehemence. Those old arch enemies, Capital and Labour, now view each other with mutual respect. Each knows full well that in this modern age defeat of one will produce collapse of both. Hence it would seem that co-operation must be the keynote if both parties are to benefit.

Such co-operation will be made that much the easier if both sides understand and appreciate the importance of the deeper psychological factors involved. Until these factors are understood, both labour and management will be merely reacting to trivial and annoying symptoms of what is in reality evidence of serious psychosocial disease. Until the disease has been eradicated, all of us will be plagued with its symptoms. It has been the purpose of this review through its historical approach to distinguish between the symptoms of the disease and the disease itself. If this purpose has to some extent been accomplished, perhaps we can look forward to an improvement in the tone and content of future labour-management relations. Such an improvement would be manifest by a shift of emphasis away from the emotional harangues over superficial symptoms, to the calm appraisal of the real disease – lack of work satisfaction.

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PARADOXICAL VALUES OF THE ERYTHROCYTE SEDIMENTATION RATE IN RHEUMATIC FEVER: A COMPARISON AMONG THREE ACUTE PHASE TESTS

Three tests of disease activity—the erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), and serum mucoprotein tyrosine (MPT)—were carried out by Harris *et al.* (*Am. J. M. Sc.*, 234: 259, 1957) in a number of situations in which the ESR may not constitute valid indication of activity of the inflammatory process in rheumatic fever. In congestive heart failure where the ESR frequently shows an anomalous return towards normal levels, the CRP was found to be apparently unaffected, as has been reported by others. The MPT, however, showed some evidence of reduction. During the administration of ACTH or cortisone at therapeutic dosage levels the ESR and the CRP were found to be sharply reduced, in confirmation of earlier reports. The MPT also appeared to be affected, although in substantially smaller degree than the other two acute phase tests. In 11 children of the adolescent age group in whom the ESR persisted at a level above the normal range for a number of months, despite clinical evidence of inactivity of the rheumatic process, the CRP and MPT were found to be within the normal range, during a three-month period of such elevation of the ESR.

It would appear that the intelligent utilization of all three tests in doubtful situations might represent a distinct forward step in the assessment of rheumatic activity.

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A QUESTION OF ETHICS

It is a particular and unchanging function of medical ethics to foster good relationships between physicians and to assist the harmonious practice of medicine. Because it is assumed that physicians are educated and cultured members of the community, codes of ethics do not customarily go into much detail but lay down broad lines upon which doctors may conduct their professional relationships.

But though the general aim of a code of ethics remains unchanging, the practice of medicine is a dynamic thing, and factors now enter into professional relationships which were unknown in the early days of national medical associations. The relationship between the specialist and the general practitioner is a good example of this change. Not so long ago, the specialist was primarily a consultant and did not see patients except at the instance of the general practitioner or family doctor. For a variety of reasons, this relationship has changed. Patients, particularly in urban districts, tend to by-pass the general practitioner and to take their complaint to a specialist in that part of the body in which they imagine their symptoms to originate. Some have no family doctor and drift rootless from specialist to specialist according to the nature of their afflictions. Others have a family doctor, but see no need to mention this fact to any other practitioner they may choose to consult. Out of this disorderly behaviour, a strain on the personal relations between physicians may develop.

Recently a committee on ethics heard the plea of an indignant allergist who stated that not uncommonly patients undergoing desensitization courses took themselves off to specialists for other and unrelated complaints and were told by the latter to stop their course of injections. The result could be confusing and even disastrous to the patient. In other cases, patients consulted a second physician and failed to mention that they were under treatment by the first, again with adverse results to themselves.

The committee to whom these matters were referred found itself in a quandary. Where there is an open breach of good manners between two physicians, the situation is clear. For example, complaints appear from time to time in the British medical press from irate general practitioners who complain that their patients disappear into hospitals and are never heard of again. Since practically every Briton has a family doctor, there is no excuse for this behaviour. The matter may go even further, for a correspondent complained in the *British Medical Journal* recently that a patient telephoned him and demanded a prescription authorized by an unknown specialist whom she had consulted. Since no communication had passed between the two physicians, the general practitioner was not unnaturally furious at this request.

However, the Canadian situation is different, and as long as our patients hawk their illnesses indiscriminately around to a variety of specialists and generalists without bothering to give a connected history, this source of irritation is likely to continue. We learn that in Britain the activities of such persons have been curtailed by certain provident societies, who insist on the patient visiting a general practitioner first and will not pay for specialist fees otherwise incurred. It is unlikely that with the different setting here, such a ruling could be enforced. Whether the growing development of health insurance will affect relationships between practitioners remains to be seen. All that can be done at present is to curtail the menace of fragmentary treatment by attempting to ascertain the full medical history of any new patient. Unless and until there is a renaissance of the concept of a "medical manager" for each family, little more can be done.

Editorial Comments

LONG-TERM ANTICOAGULANT THERAPY

The use of anticoagulants to prevent subsequent thromboses and their complications was probably suggested in the first instance by Solandt and Best,[1] but these drugs were not in widespread application for another ten years. In late 1948, Wright and associates[2] reported on 1031 patients with myocardial infarction, and found thrombo-embolic complications over three times as common in the control as in the experimental group. In both groups the incidence of complications was increased during the first four weeks. Accordingly, they advised the continuation of anticoagulant therapy for at least six weeks. The duration of this therapy has gradually increased until today there are physicians who advocate its use for life. They think of anticoagulants for the appropriate patient much as they think of insulin for the appropriate diabetic.

There is much discussion about appropriate patients; views range from none to all with a thrombo-embolic episode, real or impending. Russek[3] has felt that good-risk patients who have had a myo-

cardial infarct require no anticoagulant. Poor-risk patients have a history of previous infarction or intractable pain, or show signs of extreme shock, enlarged heart, gallop rhythm, congestive failure, atrial fibrillation or flutter or diabetic acidosis. But as Wright has shown,[4] it is often impossible to predict within the first 24-48 hours. In fourteen patients considered to be good risks, twenty-two thrombo-embolic complications occurred, with four major amputations. Thus Wright advises the use of anticoagulants for all persons with myocardial infarction, unless there are specific contraindications. He found[5] the risk of death to be greatest in the following persons in descending order: (1) age 60 or greater; (2) 10% or more overweight; (3) those with a history of congestive heart failure, diabetes, atheroma or hypertension; and (4) those with persistent congestive failure, shock or uræmia. Of these groups the use of anticoagulants reduced the risk most dramatically in the overweight, the diabetics and the elderly.

Having decided for any given patient that anticoagulant therapy is indicated, one must then consider the duration of such therapy. Suzman and associates[6] reported on two groups of patients, similar as to age, sex, symptoms, severity of illness and so forth. One group (88 patients) was given anticoagulants for three months only, though followed up for six years; the other (82 patients) was treated for a minimum of six months, extending to 76 months. The former patients suffered more than three times as many subsequent infarctions with six times the number of deaths. Over twice as many patients suffering from angina (23 as against 9) improved on long-term therapy.

Another consideration in long-term therapy is the risk of hæmorrhage at subsequent operations. Storm and Hansen[7] reported no greater hæmorrhage during, or after, mitral commissurotomy in 26 patients treated with dicoumarol than in 26 patients not given the anticoagulant. The treated group had no thrombo-embolic complications whereas amongst the untreated there were six instances.

Cerebrovascular disease has also been treated with anticoagulants. Millikan and associates at the Mayo Clinic have been studying this group for some years and reported[8] on 33 patients with intermittent insufficiency of the basilar or carotid arteries. Since the initiation of therapy these patients have suffered none of their previous episodes of transient diplopia, dysphagia, dysarthria, or unilateral motor or sensory loss. Of a further 50 patients there were 14% deaths in the treated and 43% in the control group.

Finally, long-term anticoagulant therapy has recently been discussed by Olwin and Paul,[9] who report their experience over nine years with 70 well-controlled patients. These patients had arterial or venous disease of the extremities, eyes, lungs or brain, in addition to a group with myocardial infarction. They were treated with all the usual anticoagulant preparations and some patients received two or more drugs, though not simultaneously. Contraindications to therapy are mentioned and considerable space is given to adequate control of the administration of the drugs. Unfortunately, no indication is given of the relative merits of the various agents employed, and no data are presented to indicate the results of treatment, or to suggest what might have been the outcome had anticoagulants not been used.

This type of retrospective study is thus less valuable in assessing the role of long-term anticoagulant therapy than the other work mentioned above, in which simultaneous studies of control and experimental groups have helped to indicate the place of this therapy in the management of disease.

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NEWER CARBONIC ANHYDRASE INHIBITORS AS ORAL DIURETICS

For over four years carbonic anhydrase inhibitors have been in use as oral diuretics. They constitute a welcome addition to the treatment of water retention in general, and have permitted greater flexibility in the management of such chronic conditions as congestive heart failure. The preparation best known in Canada is 2-acetylamine-1,3,4-thiadiazole-5-sulfonamide, better known as acetazolamide or Diamox. Though of comparatively low toxicity, it has been reported to have caused agranulocytosis, thrombocytopenia and other reactions well known from the use of sulfonamides. Circumoral and peripheral paræsthesias are commonly encountered, especially when larger doses are used. The search for a more potent but less toxic preparation has recently produced two compounds, on which reports are available, and which appear promising.

In Germany, diphenylmethane-4,4′-disulfonamide was developed by Wirth,[1] who reports on its pharmacological properties, its lack of toxicity and high diuretic action in rats, rabbits, cats and dogs. Meythaler and Hofer[2] treated 52 cases with this new compound, marketed as Nirexon (Bayer). Of these, 44 had congestive heart failure, seven cirrhosis of the liver, and one pituitary obesity in which Nirexon was used as an adjunct to reducing treatment. In three of the cases with cirrhosis of the liver continuous administration of Nirexon produced confusion, stupor and coarse tremor of hands and fingers. This cleared after the patients were put on a protein-free diet and intermittent

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administration of Nirexon. No other undesirable effects were observed in any of the other cases treated, even when 1 g. daily was given for 10 days. Refractoriness develops frequently with Nirexon just as it does with Diamox. Response to Nirexon was poor in 37% of cases. Failure to respond to carbonic anhydrase inhibitors is explained by the authors as probably due to intracellular sodium retention, which was found by Herken in all these resistant cases, even after prolonged low sodium diet and correct digitalization. Increased aldosterone production is said to occur after prolonged use of a low-sodium diet, and this may tend to perpetuate intracellular sodium retention even in the presence of normal serum levels of sodium.

In New England, p-sulfamyl-2-hydroxyethyl-carbanilate, identified as W-1548, was tested by Hirshleifer and his colleagues[3] in 45 patients; 38 patients had cardiac disease, five had cirrhosis of the liver, one had myxœdema and one chronic glomerulonephritis. In 10 cases this compound was able to replace mercurial diuretics, in 12 it permitted reduction of the dose of mercurial diuretics or proved otherwise superior to other oral diuretics, and in a further 11 cases its action was equivalent to that of other oral diuretics. Of the 12 cases which failed to respond to W-1548, seven were refractory to all other diuretics including mercurials. Excluding these seven cases, 86.9% showed some diuretic response and 13.1% failed to respond. One patient with cirrhosis of the liver was inadvertently given 6 g. of the compound for two consecutive days and lapsed into coma from which he recovered after discontinuation of the drug. In three patients minor side-effects were observed but did not necessitate discontinuation of the treatment. Repeated laboratory investigations of urine and blood failed to show any evidence of untoward reactions from the use of this compound. Refractoriness to the drug was overcome by intermittent administration, such as 1 g. daily for two to five days followed by a rest period of two to four days. W-1548 was found by the authors to be more effective than Diamox in four cases and to equal it in six other cases.

It is of more than passing interest that administration of carbonic anhydrase inhibitors in some patients with liver disease was followed by precoma and coma. It is well known that this clinical picture can occur whenever large amounts of nitrogenous material are introduced into the gut (hæmorrhage, high protein intake) or ion exchange resins or ammonium chloride make larger than usual amounts of ammonia available for intestinal absorption in the presence of liver disease. Carbonic anhydrase inhibitors prevent renal excretion of ammonium ion, thus producing hyperammoniæmia. If the liver is unable to detoxify all the ammonium, or if some of it reaches the general circulation through a portacaval short-circuit, it is able to exert its toxic effect on the central nervous system. Although there is no conclusive evidence as to the mode of action of ammonia on the central nervous system, its etiologic role in the production of hepatic coma is gaining wide acceptance.

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NEW ANTITUBERCULOUS DRUGS

The recent precipitous drop in mortality and decline in morbidity from tuberculosis have fostered the erroneous impression, in lay and professional circles alike, that this disease does not constitute a problem and is no longer worthy of our attention. Matters have come to such a pass that discussion of the management of tuberculosis is no longer acceptable except in terms of a mass exercise in disease control. Happily, however, there are still centres in which a sense of proportion has not been completely lost, and in these the search for new antituberculous agents and combinations of such agents is being rigorously pressed.

Since the advent of chemotherapy, the best results along these lines have been obtained by repeated chemical modification of existing agents and sequential therapeutic trial of these modifications; and the most recent though qualified successes in tuberculotherapy have stemmed from this technique.

The most promising of these newer agents is a chemical modification of isoniazid known as Verazide.[1, 2] This has the chemical structure 3:4-dimethoxy-benzal isonicotinyl hydrazone, and its relationship to isoniazid is obvious. Although in a strongly acid medium it is hydrolyzed to isoniazid and veratric aldehyde, its efficacy does not appear to depend on this feature, since when administered to humans in the uncoated compressed tablets, 60% remains unchanged.

Because of its strong penchant for tissue destruction, Verazide cannot be given intramuscularly. This is unfortunate for by virtue of its low solubility it would otherwise be admirably suited for depot dosing. It would appear that milligram for milligram Verazide is not a more potent antimycobacterial agent than isoniazid. Its unique value lies in the fact that its chemotherapeutic index is more favourable than that of isoniazid, that is, its therapeutic and toxic doses are further removed from one another. This point should not be too much laboured however. To the practising phthisiologist as distinct from the pharmacologist, the toxicity of isoniazid—apart from its effect on bodily stores of pyridoxine—is an extremely variable quantity; and patients can safely be given much larger doses than usually recommended if their pyridoxine stores are concurrently replenished. Verazide will therefore have to demonstrate its special efficacy in extended clinical trial, as has been the case with other antimycobacterial agents.

Another rather interesting line of approach in this field has been the therapeutic trial of actual chemical combinations of standard antimicrobial agents, such as, for example, the PAS salt of isoniazid.[3, 4] Unfortunately the results of such trials indicate that no such combination can contain sufficient PAS to prevent or delay the emergence

of resistant strains of tubercle bacilli. Thus bacterial resistance to the PAS salt of isoniazid closely mirrors that to isoniazid alone; treatment with such a combination should therefore be regarded as equivalent to treatment with isoniazid alone.

In spite of the lack of unqualified success in these most recent efforts, it is heartening to note that these efforts are continuing—despite public and professional apathy, and in the face of the erroneous official assumption that the problems of tuberculosis will be solved (as they never were in the past) by efforts in the epidemiologic field alone.

S. J. SHANE

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PYELONEPHRITIS AND DRUGS

During the last 20 years chronic pyelonephritis has been increasingly recognized as a common disease, and as an important cause of Bright's disease. The questions of the pathway of infection, the most important pathogens, and the puzzling persistence of bacilluria or repeated recurrence in face of what appears to be adequate treatment, all remain to be answered, but the majority of writers on the subject accept the entity of chronic pyelonephritis.

Non-obstructive chronic pyelonephritis is thought to be due to infection by the hæmatogenous or ascending route, though direct extension and lymphatic spread are also thought to occur at times. Dissenting voices now come from German-Swiss clinics. According to O. Gsell and his co-workers[1] in Basel the name pyelonephritis points to the renal pelvis as the primary seat of the disease, which is not at all the case. They quote Zollinger, who did histopathologic work on this entity, as defining it as "nonpurulent inflammation of the renal interstitium with sclerosis of the interstitial tissue and the basal membrane of the tubules". Accordingly they consider the name "primary chronic interstitial nephritis" to be more correct, and this name is now used in the clinics and laboratories of German-speaking Switzerland.

The frequency with which this disease has been associated with prolonged daily intake of phenacetin-containing drugs has led some writers to name it "phenacetin nephritis". This Gsell and his co-workers criticize, for other chronic toxic conditions (amyloidosis, chronic inflammatory lesions) can produce interstitial nephritis. On the basis of 28 carefully investigated cases (of which 7 came to autopsy and showed the typical renal changes) and the examination of a further 13 patients with known prolonged phenacetin abuse but without obvious renal damage, as well as experimental studies, they postulate that: (1) The regular intake of large doses of phenacetin causes damage to erythrocytes, as evidenced by shortened lifespan of tagged erythrocytes. (2) If this phenacetin abuse continues over long periods, renal damage will result. Just as acute interstitial nephritis results from excretion of large amounts of abnormal hæmoglobin or myoglobin (transfusion reaction, crush syndrome), so chronic interstitial nephritis results from excretion of small amounts of abnormal hæmoglobin (sulf- and met-hæmoglobin). (3) Probably bacterial infection or some other additional damage is required to precipitate the nephritis.

So far this relationship of interstitial nephritis with phenacetin abuse has been described only in Switzerland. If statistics are correct the per capita consumption of phenacetin in the U.S.A. equals that of Switzerland, and one would expect before long reports of this relationship from our side of the Atlantic. Possibly patients with what is commonly known as chronic pyelonephritis should be more thoroughly questioned as to intake of toxic substances, such as phenacetin.

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LONG-TERM PREDNISONE THERAPY IN RHEUMATOID ARTHRITIS

There now seems to be little doubt that prednisone and prednisolone are superior to cortisone, hydrocortisone and corticotropin in the long-term management of rheumatoid arthritis. The major advantages of these newer steroids lie chiefly in the absence of electrolyte disturbance following their use. Neither significant sodium retention nor potassium loss was noted by Cohen and his colleagues[1] during a three-month to one-year period of treatment of rheumatoid arthritis in 132 patients. Perhaps dependent on this point is the lack of development of significant hypertension in previously normotensive patients, and the disappearance, while on prednisone therapy, of hypertension that had developed in patients while on cortisone therapy.

One should not, however, be lulled into a false sense of security by these statements, and proceed on the assumption that these steroids are completely without undesirable side-effects. In at least 20% of such patients, the exhibition of these hormones will result in a demonstrable diminution of adrenocortical function. Acne and hirsutism will be noted in a small number, and a moon facies will be detected in at least half of all patients treated with these drugs.

Patients with diabetes will still require careful management and additional insulin in certain cases; and those with active or inactive peptic ulcer will still require special consideration. Prednisone can also reactivate quiescent tuberculosis if concurrent antimicrobial therapy is not recommended.

It would seem, therefore, that, while these potent steroids display distinct advantages over their earlier counterparts, they are still far from representing the ideal in the treatment of rheumatoid arthritis. There should therefore be no lag in the continuing search for more effective and less dangerous therapies.

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Medical News in brief

HYPNOTIC SUGGESTION FOR DUMPING SYNDROME

The *Journal of the American Medical Association* for December 14, 1957, carries a report by Leonard and his colleagues from Minneapolis of the treatment by hypnotic suggestion of a group of 16 patients suffering from an incapacitating dumping syndrome after gastric resection. Patients were first subjected individually to hypnotic suggestion on several occasions and then to group hypnotic sessions. Relief was complete or nearly complete in every case. The patients improved from the first treatment and gained complete relief usually after three to five treatments, with improved appetite and return to gainful employment. The authors have been favourably impressed with these preliminary results.

B.C.G. IN THE U.S.S.R.

The general principles of prevention and treatment of tuberculosis are universally accepted, the only area of controversy still remaining in this field being B.C.G. vaccination. It is of interest to know the stand on this question in the U.S.S.R. In a review on the occasion of the 40th anniversary of the October Revolution, Z. A. Lebedev (*Klinitcheskaya Meditsina*, 6: 6, 1957) states that B.C.G. vaccination was introduced in the U.S.S.R. 32 years ago. It is compulsory and is according to French and Indian observers the most extensive and complete of any antituberculous vaccination program in the world. Infant mortality from tuberculosis has dropped two to four times because of vaccination alone. Morbidity was found to be five to six times less common in vaccinated groups than in non-vaccinated persons living under similar conditions, and in youths the reduction was sevenfold. Pochitonov and others demonstrated that the disease runs a much milder course if acquired by vaccinated persons, frequently without local manifestations. The present consensus being that immunity decreases after three to four years, the Ministry of Health has ordered re-vaccination of healthy children at the ages of two, three, seven, 10, 14 and 18 years. Vaccination of non-infected adults has also been introduced. Oral vaccination with massive doses of B.C.G. is at present under intensive study.

ISLET CELL TUMOUR AND PEPTIC ULCER

A recent *Lancet* editorial (2: 1151, 1957) calls attention to a new syndrome consisting of pancreatic islet-cell adenoma, severe peptic ulceration, and gastric hypersecretion. The association between some pancreatic islet-cell adenomas and severe, progressive and often atypical peptic ulceration was recognized by Zollinger and Ellison in 1955. At least 26 instances of this association have now been described. (MacKenzie and his associates from Edmonton described two cases at the October meeting of the Royal College of Surgeons in Montreal.) In these cases the adenoma cells did not contain beta cell granules and, while the presence of alpha cell granules has been reported in some cases, no evidence of glucagon hypersecretion was found in these patients.

It is possible that the pancreatic adenomas of Zollinger and Ellison may cause mechanical obstruction, but the accumulating evidence is more in favour of a hormonal link. Their incidence remains to be established, but they are thought to be less common than insulin-secreting tumours, though Pease reported no less than 8 in 500 consecutive necropsies. In almost half the recorded cases the tumours were multiple. Most of these tumours sooner or later proved malignant, but they grow slowly.

In the series reviewed by Ellison 22 patients underwent surgical treatment, 4 for a known pancreatic tumour and 18 for peptic ulceration. The associated pancreatic tumour was recognized at operation in 9 (at the first operation in 4 and at a subsequent operation in 5). A further 9 patients, in whom the tumour remained unrecognized until necropsy, underwent 23 operations, with an average postoperative survival of less than two years. Recurrent ulcers with complications caused the deaths. In these cases there was a massive and sustained outpouring of gastric juice. In some cases the overnight volume exceeded 2 litres, even on a rigorous medical regimen and after subtotal gastrectomy and vagotomy.

Despite the uniformly stormy postoperative course and the high mortality, Ellison's review of the case material shows that a combined procedure for tumour and ulcer offers the patients the best chance. Zollinger recommends that whenever a pancreatic tumour is recognized its removal should be supplemented by total gastrectomy, combined with resection of the body and tail of the pancreas in all patients who fit the syndrome clinically but in whom no tumour can be found at operation.

A NEW ANTICOAGULANT: ANISINDIONE

A new drug of the indanedione type called Anisindione (2-p-anisyl-indanedione-1,3) has passed the stage of animal experimentation and is now in clinical use. It was recently administered for a total of 1198 patient-days to 52 patients suffering from arteriosclerotic heart disease, rheumatic heart disease, postphlebitic syndrome, acute thrombophlebitis and similar vascular lesions (K. Lange *et al.*, *Am. Heart J.*, 55: 73, 1958). Using the Quick one-stage method for determination of the prothrombin activity, it was found that an initial dose of 200 mg. decreased the prothrombin activity to the 75% level within six hours and to a maximum of 40% after 30 hours; it had no more effect after 110 hours. The most satisfactory method for starting therapy was to administer 500 mg. of the drug on the first day, followed by 300 mg. on the second and fourth days, with nothing on the third. The drug proved to be quite safe in its effective dosages, and remarkably free from toxic effects on the hepato-biliary apparatus and marrow. The effect was completely reversed by the administration of 50 mg. of phytonadione intravenously. This vitamin does not give rise to a period of resistance to the drug, as is encountered with dicoumarol. Switching from dicoumarol to Anisindione can take place smoothly and without jar.

(Continued on advertising page 57)

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MEDICAL FILMS

CONTINUING the listing of available films on medical and related subjects, we list below additional films. These films are held in the National Medical and Biological Film Library and are distributed by the Canadian Film Institute, 142 Sparks Street, Ottawa, Ontario. The evaluations have been prepared by Canadian specialists in the subjects of the films, under the Medical Committee of the Scientific Division of the Canadian Film Institute, which is headed by Dr. G. H. Ettinger.

ANATOMY

The Development of the Chick (193-) Sound, B & W, 22 minutes.

Produced by Gaumont-British Instructional Limited. Technical Advisers: Dr. Julian Huxley and H. R. Hewer, M.Sc.

Description.—This instructional film illustrates the embryology, hatching and development of the chick. The structure of the egg is examined and the early development of the blastoderm, the formation of the primitive streak, neural groove, brain, foregut, heart, eyes and area vasculosa are shown in detail. The cervical flexure and amnion formation are shown. The formation of the allantois and limb buds, the rapid growth of the whole embryo, the development of wings, feet, beak and feathers, and the use of the allantois and yolk-sac are described and illustrated. Hatching is seen in detail, and the subsequent growth of the chick to maturity is illustrated at various stages.

Appraisal (1947).—An excellently arranged and organized film, recommended for university biology classes, pre-medical students, medical students in the pre-clinical years, and general scientific audiences. Suitable also for high school classes in biology and for nurses and medical auxiliaries.

Availability.—National Medical and Biological Film Library ($3.00). Purchase from J. Arthur Rank Film Distributors (Canada) Limited, 277 Victoria Street, Toronto, Ontario.

Development of the Nervous System (1939) Silent, B & W, 18 minutes.

Produced by Joseph J. McDonald, M.D. Technical Adviser: Dr. L. B. Arey, Department of Anatomy, Northwestern University Medical School.

Description.—This instructional film illustrates the development of the nervous system in the mammalian embryo. The film employs animated diagrams throughout to present in detail the embryonic development beginning at the primitive streak stage.

Appraisal (1945).—This is a very well done film, although it might have been improved by longer time on some shots, particularly the explanatory subtitles in the latter part. It is recommended for college and university students in medicine and zoology, and for interested scientific audiences.

Availability.—National Medical and Biological Film Library ($1.50). For purchase apply to Dr. L. B. Arey, Department of Anatomy, Northwestern University Medical School, Evanston, Illinois.

Development of the Testis and its Associated Structures (1941) Silent, Colour, 33 minutes.

Produced by Alfred H. Iason, M.D., Brooklyn, N.Y.

Description.—An instructional film illustrating the embryonic development of the human testis and its associated structures. The film employs animated diagrams throughout and shows the descent of the testes from 30 days to six months. Normal descent through the inguinal canal into the scrotum is shown, noting the role of the gubernacula and their functioning, normal and abnormal. Anomalies such as hernia and hydrocele are described.

Appraisal (1945).—The animation is excellent and the simplicity of the drawings lends clarification. The film is up-to-date and is recommended for students in zoology and medicine and for any interested medical audiences. It is inappropriate for other than medical and scientific groups.

Availability.—National Medical and Biological Film Library ($4.00). For purchase apply to Alfred H. Iason, M.D., 41 Eastern Parkway, Brooklyn, N.Y.

Dividing Cancer Cells in Vitro (1929) Silent, B & W, 7 minutes.

Produced by Dr. Warren H. Lewis, Department of Embryology, Carnegie Institution of Washington, Baltimore, Md.

Description.—A record film, demonstrating several mitotic divisions of cancer cells *in vitro*, shown by time-lapse ciné-photomicrography. Among the divisions seen are two triploid divisions.

Appraisal (1947).—The fine points of cell division are beautifully illustrated in this film. It is recommended for pre-clinical and clinical medical students, and is suitable for other interested medical or scientific groups. Addition of a soundtrack would improve the usefulness of the film, which requires a running explanatory commentary by the lecturer.

Availability.—National Medical and Biological Film Library ($1.50). Purchase from the Wistar Institute of Anatomy and Biology, Woodland Avenue and 36th Street, Philadelphia 4, Pa.

Dividing Normal Adult Rat Fibroblasts in Tissue Cultures (1929) Silent, B & W, 7 minutes.

Produced by Dr. Warren H. Lewis, Department of Embryology, Carnegie Institution of Washington, Baltimore, Md.

Description.—A record film, demonstrating mitotic division of normal fibroblasts in tissue culture. A series of different mitoses is presented by time-lapse ciné-photomicrography, showing the process of cell division in typical mammalian cells. There are no explanatory subtitles.

Appraisal (1947).—This is a good film, but requires a running explanatory commentary by the lecturer. The fine points of cell division are beautifully illustrated. The film is recommended for pre-medical and pre-clinical medical students, and is suitable for any interested medical or scientific audience.

Availability.—National Medical and Biological Film Library ($1.50). Purchase from the Wistar Institute of Anatomy and Biology, Woodland Avenue and 36th Street, Philadelphia 4, Pa.

The Early Development of the Rabbit Egg in Vitro (1929) Silent, B & W, 16 minutes.

Produced by Drs. Warren H. Lewis and P. W. Gregory, Department of Embryology, Carnegie Institution of Washington, Baltimore, Md.

Description.—This film demonstrates, through time-lapse ciné-photomicrography, the early development of the rabbit ovum. Eggs are seen at various stages from 10 hours to 108 hours after fertilization, showing cell divisions and early embryological development.

Appraisal (1947).—A clear, interesting presentation despite its age. The fine points of cell division are beautifully illustrated. The brevity of the subtitles makes necessary a running explanatory commentary by the lecturer. Recommended for medical students in the pre-clinical years and for general scientific audiences. Suitable for other interested medical and scientific groups.

Availability.—National Medical and Biological Film Library ($1.50). For purchase apply to the Wistar Institute of Anatomy and Biology, Woodland Avenue and 36th Street, Philadelphia 4, Pa.

(To be continued)

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REVIEW ARTICLE

ALLERGY IN CHILDREN VERSUS ALLERGY IN ADULTS*

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FOR A LONG TIME now it has been recognized that, although children and adults suffer from the same diseases to a great extent, there are sufficient differences between the manifestations of these diseases in the two age groups to render necessary the separation of pædiatrics from internal medicine. Children are much more labile in their response to illnesses; in general they become acutely ill much more rapidly but recover from acute illnesses more rapidly. They have a good deal less immunity to infections. Their water and electrolyte balance is much more easily upset, and furthermore they must at all times meet the nutritional requirements for growth as well as those for maintenance and repair. It is therefore not surprising that allergy as it affects infants and children has many differences from allergy as it affects adults.

PROGRESSION OF SENSITIVITIES

One of the most marked differences between the two is the progression of developing sensitivities. In adults sensitivities are relatively fixed. This does not mean that once a person reaches adulthood he cannot develop new sensitivities; the reverse is frequently true. None the less an adult who is seen because of a clinical allergy will probably have some definite entity such as asthma, hay fever, or eczema which may require years of treatment; the sensitivities such as those to inhalants or pollens, which may be determined at the time he is studied first, will explain the illness over the period of years and re-testing is commonly not necessary.

In the infant and child on the other hand, a rapid change in the sensitivities is to be expected. Sensitization in the first place may begin *in utero*, as has been adequately worked out by Ratner and his group.[12] This is usually to foods and may be manifested clinically by the infant's having an allergic reaction on his first exposure to the food after birth. Further sensitivities to foods may be acquired early in life via the mother's milk or from dietary foods. In general terms, foods are the most common cause of allergy during the first two years of life, but during the second year the inhalants and epidermals become more important, and after infancy in some cases the pollens and moulds start to cause clinical manifestations. All cases of course do not go through this progression of sensitivities. The patient may remain clinically sensitive to foods for years without developing other sensitivities, but the common course of events is the one outlined. For this reason partial re-testing may be required periodically to detect these new sensitivities.

PROGRESSION OF CLINICAL ALLERGIES

The same type of progression can be observed in the development of new clinical allergic syndromes. At the time his allergy becomes severe enough to require study, the adult may have one or more allergic diseases which he tends to keep until such time as treatment has relieved him sufficiently that treatment may be stopped. On the other hand, the infant and small child tend to develop during treatment other allergic diseases subsequent to the one for which they come for treatment. The common manifestation in early infancy is eczema. Over half of the infants who have moderately severe or severe eczema in infancy go on to develop respiratory allergy in the next few years, either asthma, hay fever or allergic rhinitis.[11] The eczema may either disappear or remain at the time of development of the respiratory allergy. Similarly, asthma is apt to come on earlier than hay fever and the infant may go through the progression of eczema, later asthma, and later hay fever with or without perennial allergic rhinitis.[11] Of those children who develop hay fever first, approximately 25% soon develop pollen asthma.[2]

PROGNOSIS

In many cases the prognosis also differs in children and in adults. Many eczemas in infancy and childhood disappear. These may disappear completely, particularly in the mild cases, without the subsequent development of other allergic manifestations. The more severe ones, as has been pointed out, may disappear only to be replaced by other allergic manifestations. Many, of course, are persistent enough to require prolonged treatment.

Eczema in the adult, on the other hand, is very apt to be extremely chronic in spite of adequate treatment according to our present standards. This is not surprising when one considers that a great many of these cases date from infancy or childhood and therefore by definition are the ones which persist in that age group and thus belong to the more treatment-resistant group.

Similarly, asthma has a much better prognosis in the infant and child. Over 90% of these cases do extremely well with adequate treatment,[15] and occasionally one will clear with no treatment at all. These patients are not cured, in the sense that they may have to avoid certain allergenic substances to which they are known to be sensitive, but none the less over 90% can after a few years of treatment be brought under control well enough to lead fairly normal lives with only minimal symptoms provided they avoid certain allergens. The prognosis for asthma, particularly in those over 40 years of age, is not nearly as good. Many of these

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patients give negative skin tests and are said to suffer from intrinsic asthma, no demonstrable external allergens such as house dust being present. They do not respond nearly as well to our present methods of treatment, and since this is a common type of asthma in the adult the percentage of good results is greatly lowered. Also adults are more apt to suffer from chronic asthma, which does not have as good a prognosis as the paroxysmal type at any age. Adults who suffer from so-called extrinsic asthma can be expected to do reasonably well, and in this sense are more like the childhood group.[14]

Hay fever and perennial allergic rhinitis may also be expected to respond better to treatment in infants and children, because these patients often are put under treatment earlier, before severe and often irreversible lesions have appeared in the mucous membrane of the nose.

The prognosis for gastro-intestinal allergy is also better in infants and children, since they are more prone to have acute reactions to foods, thus definitely implicating the responsible food, which can be removed from the diet. Particularly in infants, it is also much easier to control the diet, and the diagnosis is obviously much simpler early in life when there are relatively few foods in the diet.

Gastro-intestinal allergy in the adult, on the other hand, is much more apt to be manifested by chronic symptoms which are harder to diagnose, requiring the use of complicated elimination diets and long-term observation for control. Treatment in adults is further complicated by the fact that so many adults eat their meals away from home where the diet cannot be as adequately controlled.

Differential Diagnosis

Differential diagnosis also varies in difficulty in the two age groups. Atopic dermatitis or eczema in infants and children is usually relatively easy to diagnose, although it may be confused with seborrhœic dermatitis, contact dermatitis, fungus infections, infectious eczematoid dermatitis and scabies.[7] The rash is much more apt to be seen early in its typical form and a definite diagnosis made. In adults the rash may have been present for years before the patient first comes for treatment and may not be as typical. In addition the factors which can cause contact dermatitis are much more numerous in the adult and add greatly to the confusion in the differential diagnosis.

On the other hand, the differential diagnosis of asthma is much more apt to be difficult in the infant or very small child than in the older child or adult. In the first place the diagnosis of asthma depends on repetitive attacks of wheezy breathing; a history of these will almost always be obtained when an older child or adult comes for treatment. Infants or very small children are likely to be seen during the first attack of wheezing, and there are a great many other non-allergic causes of wheezing in infants and children such as bronchitis, bronchiolitis, bronchopneumonia, laryngotracheobronchitis, whooping cough, congenital laryngeal stridor, double aortic arch, aberrant left subclavian artery, enlarged thymus, aspiration pneumonia, cystic fibrosis of the pancreas, stridor due to cerebral palsy and salicylate intoxication, to mention only a few. When the infant is seen during the first bout of one of these, it is extremely difficult to make an accurate diagnosis; only on further observation can a correct diagnosis be arrived at in many cases. Since upper respiratory infections are much more common in children than in adults, hay fever and perennial allergic rhinitis are much more apt to be mistakenly diagnosed initially in children as infections.

Skin Tests

Skin tests are more likely to point to the cause of allergic disease in children than in adults. An exception to this is the very small infant in whom, although the skin is sensitive for skin testing, the antibody often is not fixed in the skin until several months after clinical sensitivity has developed and therefore skin tests may be negative. Food tests are more apt to be reliable in children than in adults because many of the positive tests clinically significant in childhood will persist into adult life after clinical sensitivity has gone, thereby giving false positive tests which may be misleading in interpreting the patient's condition. The vast majority of children with asthma, hay fever or perennial allergic rhinitis give positive skin tests with the etiologically significant inhalants and pollens. This is not true particularly of asthma in adults, where a large number—especially in the older age group—have intrinsic asthma and give negative skin tests.

Drug Allergy

Allergy to drugs is not nearly as common in children as in adults, for two reasons. Children are not exposed to the multiplicity of drugs taken by adults; also, if sensitivity is going to develop it usually takes several administrations of the drug and by the time this has happened the patient may have grown up. This is seen particularly with penicillin to which allergy is relatively uncommon in children but extremely common in adults.

Psychosomatic Factors

One very important difference between the two age groups is that of psychosomatic factors. These operate at any age but in most cases are a good deal more important in adults than in children. The child with a chronic disease may have very important psychosomatic factors operating in that he resents the disease, resents the help which people try to give him for it, and particularly resents taking medications and facing restrictions in his activity. However, he does not have the chronic worry of economic loss, fear of prolonged disability, etc., that the adult has with similar

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disease. This change in attitude is very well exemplified by watching a child with severe symptoms approach the age of puberty when his attitude becomes much more serious from a psychosomatic point of view as he realizes what it is going to mean if symptoms continue into adult life.

INFECTION

In infants and children, acute infections precipitating attacks of respiratory allergy, especially asthma, are more important than in adult life. The usual course of asthma in the infant or child is that attacks are precipitated by respiratory infections due to bacterial allergy, or due to a trigger mechanism bringing on symptoms caused by food, inhalant or other sensitivities, or perhaps by a combination of both. Later on, attacks come on without apparent acute infection. These factors also operate in adult life to a lesser extent, but here chronic infection—particularly focal infection—is even more important than in children, as exemplified by intrinsic asthma which is relatively rare in children.

IRREVERSIBLE EMPHYSEMA

Irreversible emphysema is not nearly as common in children as in adults since it usually takes years to develop; for this reason the carbon dioxide intoxication syndrome which may cause death in the asthmatic is confined mostly to adult life.

PROPHYLAXIS

It is in the possibilities for the prophylaxis of allergy that probably the most important difference exists between younger and older persons. By the time adults are seen, their allergy is usually fairly well established and must be treated as it presents. While this is true of many children, there is also a very important field of prophylaxis of allergy which is probably the most important function of the pædiatric allergist.

If a woman has produced an allergic child, and particularly if that child has shown food allergy shortly after birth, during subsequent pregnancies she should remain on a diet consisting only of ordinary foods in ordinary amounts.[1, 13] Milk should be restricted to two glasses a day with supplementary calcium. Wheat should be restricted to the equivalent of two slices of bread a day. She should eat no eggs as such, although she may eat foods containing small quantities of egg. She should not eat any of the unusual foods such as shellfish and strawberries and should not give way to cravings. All infants should be breast fed from the time of birth; and if the mother has reason to be on the diet outlined above during pregnancy, she should remain on that diet while breast feeding the baby. No infant in the newborn nursery should be given a cow's milk supplement except on orders from the attending physician. Any required supplement should consist only of lactose water or some such sugar solution. If a cow's milk supplement is required, the infant should be given only evaporated milk, since this is a great deal less allergenic than ordinary pasteurized milk.[10] Once the cow's milk formula has been started it should be continued daily, since occasional feedings of cow's milk are much more apt to cause sensitization than repeated daily feedings.[10] If any symptoms do appear which may be attributed to cow's milk or to any other food subsequently added, the food should immediately be withdrawn, and then tried again in a few days to establish the diagnosis early. If the diagnosis of sensitivity is established, the food should be omitted from the diet for several months and then slowly added again.

Solids should not be added too early, and the less allergenic solids should be added first. It is rarely necessary to add cereal to the diet before two months of age. Rice cereal should be added first; barley and oatmeal cereals may be added subsequently. Wheat cereals should not be added until five or six months of age. Vegetables may be added at three or four months. It is best to start with carrot or squash, as these rarely cause difficulty. Only one should be added at a time and the mixtures which the baby food manufacturers prepare should not be used unless the infant has received everything in the mixture except one new food. Fruits may be added at four or five months and it is best to start with applesauce or banana, which rarely cause trouble. Meats should be added around five months. Beef is quite suitable if milk is tolerated. Lamb is also well tolerated. Pork and fish, which the baby food manufacturers are now preparing, should be left for several months later. Egg in any form should not be given before six months of age, and then only hard-boiled egg yolk should be given, either alone or mixed with other foods. Egg white should not be given until one year of age and then only in a well-cooked form.

During illnesses, particularly those involving the gastro-intestinal tract in infants and children, the diet should consist entirely of relatively hypoallergenic foods, since at these times the undigested protein molecule is much more apt to pass into the blood stream where it may result in antibody formation with subsequent allergy.[5]

Glaser and Johnstone[1, 3, 4, 8] have done considerable work on this problem, carrying it one step further. They strongly advise that if infants from allergic families cannot be breast fed, they should be given a soybean supplement in place of cow's milk and should be kept off cow's milk for the first six months of life during the period which they call physiological immaturity of the intestinal tract. In a large series they demonstrated that these infants were much less likely to become sensitive to cow's milk than those put on it at birth. They also found from an analysis of their data that these children had a much lower incidence of other allergic manifestations such as respiratory allergy in later life than did the children given cow's milk

from birth. This study has met with a considerable degree of criticism,[6, 9] the chief criticism being a lack of satisfactory controls, so that the conclusions, particularly that relating to the decreased incidence of other allergic manifestations such as asthma, are unsound. Obviously a study with a completely controlled series is extremely difficult, but whether or not one believes that such prophylactic measures will prevent subsequent development of other allergic manifestations, it is perfectly obvious to anyone who has cared for a great many infants from birth that the incidence of allergic manifestations, particularly gastrointestinal allergy and dermal allergy in this early age group, can be reduced considerably and their severity minimized by dietary methods similar to those outlined. The observation on the subsequent development of other allergic manifestations will require further clarification.

A great many other things can be done which would logically decrease or at least minimize the chances of development of other allergies. Infants of allergic families or infants with previous allergic manifestations should have their environment carefully controlled; this should decrease the chance of their developing subsequent sensitivities. For example, the infant's room should be kept relatively dust-free. Allergens such as wool and silk should be kept away as much as possible. The mattress should be covered in plastic or some other impervious material. Bedding and night clothing should be largely cotton. The infant's toys should be wood, rubber or rubber-stuffed, nylon-covered toys rather than the usual fuzzy cotton or kapok-stuffed animals which are sold. The heating system in the house should be made as dust-free as possible. This usually can be done by changing the filters in the furnace three or four times a winter rather than leaving the same filters in year after year. Unnecessary dust-collecting objects should not be allowed in the room. The cupboards should be kept relatively clear of dust-catching objects and the room should be cleaned thoroughly so as to keep it as free of dust as possible. Animals and birds should not be allowed in the house, and exposure to these should be kept to a minimum.

Since we know that these precautions will considerably relieve clinical manifestations of allergy, it is logical to assume that they will decrease the chance of allergic manifestations developing. The development of clinical allergy is known to have as a factor the degree of exposure, and therefore it is perfectly reasonable to suppose that allergy is less apt to develop if exposure is kept to a minimum.

In adult life these factors are not as easily controlled, because of the ways of life into which the patients have grown and also because the patient is usually not seen until his allergy has developed.

COMMENT

Nothing in this discussion should be construed to imply that there is a sharp dividing line between allergy in infants and children on the one hand, and allergy in adults on the other. There is no sharp line of division. The differences are of degree rather than absolute. However, it is imperative that all allergists recognize these differences of degree if they are going to diagnose and treat their patients properly. In an individual patient several of these differences may be important, and it is therefore always important to keep the patient's age in mind when planning treatment. Most important of all, the question of the prophylaxis of allergy must be borne in mind when dealing with infants and children, since this is the field of allergy in which the most gratifying results can be obtained.

SUMMARY AND CONCLUSIONS

Although infants, children and adults suffer from the same allergic diseases, there are a great many differences between allergy as seen in infants and children on the one hand and in adults on the other. The differences are of degree rather than absolute. These differences are found in the progression of sensitivities, the progression of clinical allergies, prognosis, differential diagnosis, importance of skin tests, drug allergy, psychosomatic factors, influence of infection, development of irreversible emphysema, and the opportunities for prophylactic measures. For the proper care of the allergic patient it is essential for the allergist to recognize these differences.

1421 Danforth Ave.,
Toronto 6, Ont.

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GENERAL PRACTICE

TOXIC REACTIONS TO LOCAL ANÆSTHETIC DRUGS

J. W. GREEN, M.D.,* *Esquimalt, B.C.*

MANY PHYSICIANS are not familiar with the hazards of local anæsthesia and have insufficient knowledge of the pharmacology, maximum dose recommended, and the systemic effects of these drugs. This statement applies especially to Pontocaine hydrochloride (known officially as tetracaine in the U.S.A. and amethocaine in the U.K.), used as a surface anæsthetic agent.

The toxic effects of procaine, cocaine and other local anæsthetic agents have been known for many years and the pioneers soon realized that rapid absorption of these drugs into the circulation could result in reaction.

INCIDENCE OF DEATHS

Accurate figures on the frequency of fatal reaction are not available, because many cases are not reported as such.

In 1924 and again in 1928 the American Medical Association set up a commission to study fatalities from local anæsthetic drugs in use at that time. They reported on 43 deaths in 1924 and 14 in 1928; in nearly all cases procaine and cocaine were the drugs used. Though, as a result of this survey, recommendations for safe dosage and technique were made, many deaths continue to be attributed to these and similar drugs. Since 1933, tetracaine has been added to this list.

Criep and Ribeiro[1] in 1953 reported three cases of fatal allergic reaction to procaine hydrochloride.

Adriani[2] found 10 unreported deaths from topical tetracaine used for endoscopic procedures performed over a 15-year period at Charity Hospital, New Orleans, and five others from hospitals in the same geographical area.

Richards[3] reported two deaths following application of 2% amethocaine (tetracaine) hydrochloride spray. Both anæsthetics were to permit bronchoscopy, and in both cases generalized convulsions set in within a few minutes and death followed shortly afterwards. The amount of agent used in each case was not known. The same author reported another case of a man who had a deflected septum treated by local application of an adrenaline swab dipped in cocaine crystals; he died in convulsions within a few minutes.

Jackson[4] reviewed the literature for cases of local anæsthetic reaction occurring in the U.K. Twelve fatalities from amethocaine used topically for endoscopic work were reported by various authors. Many of the deaths occurred in chronically ill or cachectic patients, two in chronic asthmatics. Jackson stated that overdosage and faulty technique were responsible for the fatal reactions.

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PHARMACOLOGY

Most of these agents in common use are nitrogenous compounds. Tetracaine and procaine are esters of para-aminobenzoic acid. Cocaine is an ester of benzoic acid. Lidocaine is not an ester but has the same chemical configuration as procaine.

These drugs all stimulate the cerebrospinal axis from above downward. After intravenous injection, the sensory areas of the cortex are stimulated, resulting in increased mental keenness and excitement. Motor activity is increased as indicated by restlessness, tremors, convulsions progressing to paralysis and coma depending on the blood level. The agents are all hydrolyzed by the liver.

FACTORS INFLUENCING GENERAL TOXICITY

Systemic toxicity of a drug depends on the amount in the circulation at any one time. This depends on the following factors:

Amount of Drug Administered, Potency and Concentration.

There is a great variation of toxicity from one agent to another. From animal experiments the following figures have been derived. If for comparison we allot to procaine the arbitrary standard of 1, that for Metycaine (piperocaine) would be 3; for cocaine 4; tetracaine 12 to 20; and nupercaine (dibucaine) 20.[6]

Though these figures are not strictly applicable to man, there is for the average healthy individual an average dose by weight for each agent. This figure will vary according to patient's age, size, state of nutrition and metabolism associated with any existing debilitating disease.

Also important is the fact that toxicity of a drug increases in geometrical and not arithmetical progression with increase in concentration. Thus a given quantity of a 2% solution has 16 times the toxicity of a similar quantity of 0.5% solution. The rule follows that one should use the lowest concentration adequate for satisfactory anæsthesia.

Rate of Absorption from Site of Injection.

The greater the vascularity of the tissues injected, the more rapid is the absorption. Areas of increased vascularity include mucous membrane surfaces of the respiratory tract, stomach and urethra, the scalp, face, neck, caudal canal, perineum and corpus cavernosum. All agents except cocaine are powerful vasodilators when used topically and without vasoconstrictors.

Regarding absorption of an agent from mucous membrane surfaces, Adriani[2] has shown experimentally that a designated quantity of a drug that results in no detectable blood level when injected subcutaneously gives levels when applied topically that are equal to 1/3 to 1/2 of that after intravenous injection.

Rate of Destruction and Elimination.

The more rapidly or easily a drug is detoxified, the less systemic toxicity it manifests. In a healthy person, detoxification is rapid, while in debilitated, cachetic patients with low basal metabolic rate (B.M.R.), elimination is delayed.

Inadvertent Intravascular Injection.

This is an accident which can be avoided by repeated preliminary aspiration tests.

Water Solubility and its Ability to Diffuse Through Mucous Membranes.

These are important characteristics of any drugs used in topical anæsthesia. For example, benzocaine is poorly soluble in water, being absorbed more slowly than cocaine or tetracaine, and reactions are practically unknown. For this reason it is popular and safe as a lubricating anæsthetic jelly among anæsthetists and urologists.

Susceptibility of Patient.

The terms "idiosyncrasy" and "hypersensitivity" are generally applied loosely. Only after errors in dosage, concentration and techniques are ruled out can one consider the above as a cause of reaction. There are no adequate tests to identify potential reactors but a previous history of a reaction should be sufficient warning.[6]

SYSTEMIC EFFECTS

It has been mentioned that these drugs stimulate the central nervous system. The other most important effect is depression of the myocardium with resultant changes in excitability, conduction and force of contraction.

Intravenous injection of procaine in animals produces characteristic electrocardiographic changes. There is heightening of the T wave, reduction in QRS amplitude, depression of S-T segment, prolongation of P-R interval, and increased width of QRS complex. Continued injection will eventually cause ventricular fibrillation.[7] This depressant effect of local anæsthetic drugs has been utilized to decrease cardiac irritability during thoracic surgery.

ALLERGIC REACTION

This type of reaction manifests itself as skin eruptions such as urticaria, contact dermatitis or angioneurotic œdema. Contact dermatitis can occur from application of anæsthetic ointments and has occurred in dentists who handle local anæsthetic drugs.

A rare histamine-like reaction, found in about 1% of severe cases, is characterized by signs of hypersecretion of lungs and bronchospasm. The three cases reported by Criep and Ribeiro[1] illustrate this type of fatal reaction. They recommend preliminary testing with local anæsthetic drugs in cases of suspected allergy, to determine whether it is safe to continue with the drug. Treatment of an allergic reaction includes administration of oxygen, sympathomimetic drugs, antihistamines and corticosteroids.

SIGNS AND SYMPTOMS

Adriani[8] recognizes two main types of toxic reaction: (1) the circulatory or depressant type; (2) the stimulating or convulsive type.

In (1) the onset is usually abrupt with pallor, feeble pulse, fall in blood pressure, syncope, increasing collapse progressing to cardiac arrest. These signs may follow the injection of a minute amount of the drug. A milder reaction with slower appearance of symptoms may occur and the patient's condition may not progress to collapse. The latter type can be controlled by administration of an analeptic and oxygen, with the patient in the Trendelenburg position. When complete collapse with cardiac arrest occurs, immediate cardiac massage and ventilation with 100% oxygen should be started. This form of reaction fortunately is less common than the stimulating variety.

(2) The stimulating or convulsive type may have an abrupt or delayed onset, may be mild or severe, and can also occur after use of a small amount of agent.

Early symptoms are nervousness, apprehension, headache, slurred speech, dizziness, blurred vision, roaring in the ears, sighing respiration, yawning, dyspnœa, tremor, twitching, and nausea or vomiting. The reaction may stop here or may progress to convulsions, paralysis and unconsciousness.

Pulse and blood pressure may be unchanged at first or there may be tachycardia with a rise in blood pressure. There may then occur a rapid fall in blood pressure with bradycardia and cyanosis. In a severe reaction due to rapid absorption of a large dose of the drug, the patient may pass rapidly from the early to the convulsive phase, and then to paralysis, coma and circulatory collapse.

The early use of intravenous barbiturates with ultra-short action will control the signs of cerebral stimulation. A sufficient amount should be injected in 25 to 50 mg. doses until convulsions are controlled, remembering that a period of 3 or 4 minutes precedes the peak of action.

Symptoms due to the vasoconstrictor agent mixed with the local anæsthetic drug may occur and may be difficult to differentiate from a true reaction. A toxic reaction from epinephrine manifests itself as nervousness, tremors, anxiety, palpitations, precordial distress, tachycardia, and rise in blood pressure and respiratory rate. Bradycardia, however, usually indicates a true local anæsthetic reaction.

TETRACAINE (PONTOCAINE) REACTIONS

Toxic effects from the use of this drug as a topical agent are common. Adriani[2] considers its potency and toxicity to be 10 times that of procaine. Thus, since for the average healthy adult the maximum injectable dose of procaine is 1 g. (1000 mg.) it follows that 100 mg. tetracaine (i.e., 5 c.c. of 2% solution) should be the maximum dose for infiltration. Since absorption from mucous membranes is so rapid, this dose should be considerably reduced for topical anæsthesia.

Consistent findings in Adriani's fatal cases include overdosage, faulty technique, lack of preparation and delay in resuscitative measures. Most cases were characterized by the abrupt, rapidly progressive collapse type of reaction without convulsions. At the Charity Hospital, New Orleans, tetracaine has been discarded in favour of cocaine as the topical agent of choice. The number of reactions reported is much smaller and they are of the stimulating, convulsive variety.

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Ireland[9] and co-workers conducted a survey of the larger otolaryngology clinics in the United States and Canada to compare the relative toxicity and potency of cocaine and tetracaine. Their findings can be summarized as follows: (1) The number of deaths from cocaine used in 31,885 cases was 3; the number of deaths from tetracaine used in 7394 cases was 4. (2) Concentration of drugs used: (a) cocaine—10% in nose and pharynx, 5% in larynx and trachea; (b) tetracaine—2% in nose and pharynx, 1% in larynx and trachea. Most clinics recommend limiting the intratracheal dose of tetracaine to 2 c.c. of 1% solution. (3) By guinea-pig experiment the mean fatal dose was determined for cocaine as 24 mg./kg. and tetracaine 7.2 mg./kg., giving a relative toxicity of tetracaine/cocaine of 3½/1. (4) Though tetracaine was generally used in 1/5 the concentration of cocaine, it was thought that tetracaine would be the safer drug but the survey did not bear this out. (5) Cocaine is by far the more popular of the two.

There are still many, however, who feel that tetracaine is too valuable a drug to be discarded. One of its best supporters is Carabelli,[10] who reports a series of 621 bronchoscopies in adults using a 0.25% solution, in a one-hand micro-atomizer and a mirror cannula permitting use of small doses of tetracaine. He used an average dose of 14.75 mg. tetracaine (0.737 c.c. of a 2% solution) with no complications. Premedication consisted of morphine or atropine but no barbiturate. In no case was a barbiturate required to counteract a reaction. In reviewing the literature, he found that all authors reporting the actual quantity of the drug used had far exceeded the dose recommended by the manufacturers. One operator was using 15 times the recommended dose for his bronchoscopies. Carabelli[10] suggests a maximum dose of 20 mg. applied in fractional doses in topical anæsthesia. Weisel and Tella[11] reported 1000 bronchoscopies using 2% solution in doses not exceeding 40 mg. They had 19 reactions—12 mild and seven severe—with no fatalities. Six of the latter were of the convulsive variety. One patient had pronounced bronchospasm and status asthmaticus. They feel that reactions can be prevented and controlled by barbiturates and that heavy premedication is indicated.

Reactions from tetracaine used in spinal or regional anæsthesia are practically non-existent. Adriani[2] reports that at the Charity Hospital, New Orleans, spinal anæsthesia was induced with tetracaine 20,000 times, with no untoward reaction. Moore[12] reported using tetracaine for regional anæsthesia in 1004 cases with one reaction and no fatality. He used the solution in concentrations varying from 0.1% to 0.5%, 0.15% being the most popular, and the total dosage of 1 mg. per lb. weight was seldom exceeded. Vasopressor drugs included in solution were epinephrine and Neosynephrin (phenylephrine). Although the injectable dose often exceeded that recommended by the manufacturer, the dilute concentration of tetracaine solution used combined with the vasoconstrictor action was responsible for freedom from reaction. In spinal anæsthesia the low dosage (maximum dose 20 mg.) and slow absorption from the spinal canal explain the absence of toxic reaction to tetracaine.

PREVENTION OF REACTIONS IN TOPICAL AND REGIONAL ANÆSTHESIA

Any patient with a history of allergy or asthma should be protected with barbiturates, antihistamines and bronchodilators.

A previous local anæsthetic reaction should be a warning to give a general anæsthetic unless there are strong indications for use of local. A previous reaction should be investigated, and if the drug is known an agent from a different chemical group should be used.

Premedication should include a short-acting barbiturate since it has been shown experimentally that it protects animals from the stimulating effect of local anæsthetic drugs. Morphine relieves pain and apprehension but should be avoided in asthmatics. The belladonna drugs, atropine or hyoscine, should be given in case a general anæsthetic is required. Food should be withheld prior to any procedures.

Avoid topical anæsthesia in inflamed or traumatized mucous membranes.

Caution the patient not to swallow the agent because of danger of rapid absorption from stomach mucous membranes.

Avoid intravascular injection by repeated aspiration tests when injecting gums, nose, pharynx, larynx, trachea, scalp, face, neck, corpus cavernosum and caudal canal. Avoid rapid injection.

Use vasoconstrictor solution with local where possible, as this delays absorption into the general circulation and does not alter the anæsthetic effect.

Use the most dilute solution adequate for anæsthesia and the minimal dose required.

Maintain continuous contact with the patient at all times. Beware of a talkative, excited patient who suddenly becomes quiet and still. A patient may pass from a stage of overstimulation rapidly to unconsciousness and depression.

Be prepared for any reaction by having immediately at hand equipment and drugs for resuscitation and a plan for action in case of cardiac arrest.

TREATMENT

If the signs of a severe reaction are at hand, place the patient in slight Trendelenburg position and administer 100% oxygen. An emergency resuscitation set with bag and mask is required for assisting depressed respirations and taking over in apnœa.

While the above is being attended to, an intravenous should be started to provide an avenue for subsequent intravenous administrations.

For hypotension give Neosynephrine in 0.2 to 0.5 mg. intravenous doses; better still, by mixing 2 c.c. of 1% solution (20 mg.) with 1000 c.c. of 5% dextrose and water, one can alter the rate of flow according to the blood pressure. Vasoxyl is another valuable vasoconstrictor which can be used in doses of 10 mg. It has minimal central nervous system side-effects.

For severe apprehension, excitement, restlessness or convulsions, give intravenously a short-acting barbiturate such as Nembutal sodium (pentobarbitone) or sodium Pentothal (thiopentone) in doses of 25 to 50 mg.

A good airway is required and endotracheal equipment should be at hand. If cardiac arrest is suspected, immediate cardiac massage is indicated.

SUMMARY

Many physicians are unaware of the hazards of local anæsthetic agents and are unprepared to cope with severe reactions.

Most local anæsthetic agents are nitrogenous compounds and all stimulate the cerebrospinal axis and depress the myocardium. Though many deaths have been reported from topical application of tetracaine, it is generally agreed that this valuable but potent agent has frequently been used in excessive amounts and without consideration of rapidity of absorption from mucous membrane surfaces.

Factors influencing general toxicity, signs and symptoms are discussed and measures for prevention of reaction and treatment are outlined.

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MEDICAL ECONOMICS

COMPREHENSIVE INSURANCE FOR PHYSICIANS' SERVICES

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COMPREHENSIVE physicians' services can be provided satisfactorily under a voluntary health insurance plan sponsored by a medical society and run on a fee-for-service basis.

This is the general conclusion derived from an extensive study of one such plan, Windsor Medical Services, Inc., of Windsor, Ontario (Canada). The study was made by the Bureau of Public Health Economics, School of Public Health, University of Michigan, under a grant from Health Information Foundation.

Data covering the experience of 1954 were obtained by interviews during 1955 with an area-probability sample of the Windsor population and with virtually all Windsor physicians. In addition, an audit of the plan's administration was made.

Less than 5% of the American population subscribes to plans that provide comprehensive physicians' benefits. Most of these plans are not sponsored by the organized medical profession, and most of them alter traditional aspects of medical practice. Windsor Medical Services has been operating successfully for 20 years. Like the typical American physicians' service plan, it is sponsored by the medical society, offers free choice of physician to subscriber, makes fee-for-service payments to physicians, and offers group enrolment of subscribers and coverage of their dependents.

Windsor itself is an urban, industrial community with a population in the study year of about 160,000 in its metropolitan area. In its population make-up and ecological and economic characteristics, it resembles the nearby city of Flint, Michigan, and other medium-sized industrial communities in the United States.

The Windsor plan emerged from the experience of the local Essex County Medical Society in operating a medical relief program for the Ontario government in the mid-1930s. Planned in 1936 and formally chartered in 1937, Windsor Medical Services obtained its first group of subscribers in July 1939.

In this initial contract the plan agreed to cover all medical and surgical services, x-ray and special services, consultations, services of anæsthetists and assistants at operations, preventive medical examinations and refractions, and confinements (including prenatal and postnatal care), in the office, home, or hospital. Excluded was care for such conditions as tuberculosis, mental illness, drug addiction, and acute venereal diseases. A waiting period of six months was specified for treatment of any pre-existing condition.

The services in the present group contract are more liberal. Radium and deep x-ray treatment are now mentioned specifically among the services offered, as are preventive inoculations and cystoscopic and bronchoscopic examinations. Exclusions, similarly, are explained more fully. Waiting periods have been specified for confinements (ten months), refractions and preventive medical examinations (twelve months), and for the removal of tonsils and/or adenoids, herniorraphy, and reparative pelvic, vaginal or perineal surgery (six months).

Although income limits had been adopted and modified during the planning period of WMS, the initial contract was offered to groups of ten or more without income restriction or additional charges. (Income limits for an individual contract then offered were set at $2000.) In 1948 the plan adopted income limits for group subscribers; physicians were permitted to make extra charges to single subscribers earning over $3000 and married subscribers earning over $6500. The only change in income limits since that time was made in 1952, when the limit for single subscribers was increased to $4000. In actual practice, not many families are affected by these income restrictions.

Since 1939 WMS has revised the premiums for its comprehensive group plan five times. In the original contract the monthly premium was $1.09 for the subscriber and for each dependent. The present monthly premium, adopted in February 1956, is $2.30 for a single subscriber, $4.90 for husband and wife, $6.50 for husband, wife, and child, and $7.90 for husband, wife, and two or more children. (In addition, most

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WMS subscribers carry hospitalization insurance with Ontario Blue Cross.)

WMS grew slowly between 1939 and 1945, when it had 7656 subscribers. Then demand accelerated, and the rate of growth was checked only by the ability of the organization to service new accounts. By the end of 1955 WMS had a total of 171,000 subscribers. In metropolitan Windsor itself, about 85% of the population is now enrolled. (During the survey year—1954—this figure was about 63%; 9% were enrolled in some coverage other than WMS; and 28% had no insurance covering physicians' services.)

ORGANIZATION

Briefly, the organization of WMS is this: Member-physicians of the corporation elect a governing board of directors, which at present consists of seven physicians and three laymen. Day-to-day operation of the plan is directed by a lay administrator, who supervises a staff of 80, and by a medical director.

Payments to practising physicians are based on a fee schedule—that is, charges the member-physicians have agreed to make for services to which subscribers are entitled. (Well over 90% of all 211 Windsor doctors are medical members of WMS.) The cost of administration has remained below 8% of income during the past decade.

In addition to the comprehensive contract, a limited contract, essentially a surgical-benefit plan but including confinements and diagnostic x-ray, was offered in 1945. This plan was designed to fill an assumed need for low-cost insurance that would be sold in conjunction with the Blue Cross plan. It had only 2158 subscribers by 1946 and only 1062 a decade later.

A pay-direct contract was also offered in 1947 to those leaving jobs in which they had had group coverage. Rates for this plan are slightly higher than group rates, but services are the same. At the end of 1955, 19,540 subscribers had elected to continue coverage after leaving their employment.

UTILIZATION

More Windsor Medical Services subscribers (68%) used physicians' services during the study year than did subscribers to other plans (58%) or those without medical care insurance (51%) (see Fig. 1). But the fact that 32% of WMS subscribers did not visit a doctor during the year, despite the absence of any financial barrier, indicates that use of medical services is by no means certain once cost factors are removed.

When only those who visited a doctor at least once are considered, each WMS subscriber received an average of 6.08 services, 38% more than the average of 4.41 for other insured and 15% more than the 5.29 of the uninsured. Thus, Windsor subscribers received a greater volume of services during the study year. However, the patterns of use—the relative proportions of light, modest, and heavy users—were substantially the same for each of the three groups (see Fig. 2).

The distribution of services in the population appeared to be stable over time; many people received only a few services and a few received many. As a result, the use of comprehensive services can be predicted statistically, so that insurance principles are applicable.

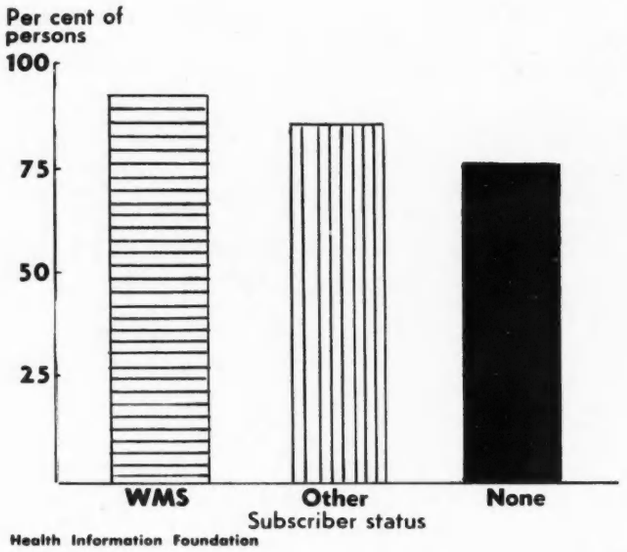

Fig. 1.—Initiation of medical care by subscriber status, Windsor, 1954.

Although WMS subscribers initiated medical care more often and used more services, they rarely incurred out-of-pocket expenses for physicians' services. In the main, costs that were incurred were due to care received before enrolling in the plan or for visits to non-participating physicians.

Although about 10% of WMS subscribers who used medical services had some out-of-pocket charges, about 75% of each of the two other groups incurred such charges. Among the uninsured, 10% had physicians' charges of $50 or more, and 7% paid $100 or more. Among subscribers to other plans, about 13% paid $50 or more for physicians' services and 4% paid $100 or more.

EFFECTS ON PHYSICIAN-PATIENT RELATIONSHIP

The doctor-patient relationship can affect both the quality and the cost of medical care. If the removal of cost barriers were to encourage patients to change physicians often or to visit a variety of specialists without professional referral, the stability of the patient-physician relationship could be damaged.

As the utilization data show, WMS subscribers follow the same general pattern as do non-subscribers

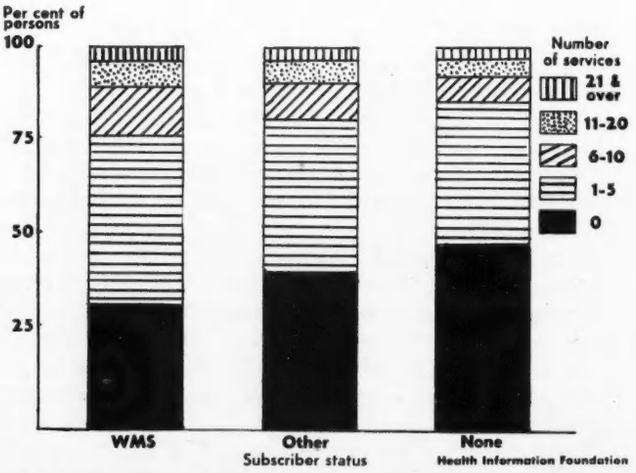

Fig. 2.—Total home and office services received by subscriber status, Windsor, 1954.

in their use of medical services. In addition, 92% of WMS subscribers have a physician whom they consider their "regular doctor", while the corresponding proportions for subscribers to other plans and the uninsured are 85 and 76%, respectively (see Fig. 3). This difference may be attributable to the increased number of WMS subscribers who seek care, but its effect is to strengthen an important element in the stability of the doctor-patient relationship.

The plan appears to have no adverse effect on the patient's satisfaction with the physician chosen. Certainly the pattern of WMS subscribers, which is essentially that of the other two groups, gives no indication of "shopping around" among doctors or other behaviour that might create an unstable pattern of care. Most people in all three groups saw only one physician during the year—typically, a general practitioner. Of those who saw two physicians, about a third saw two general practitioners, 10% or less saw two specialists, and the rest saw one of each. The relatively few people who visited three or more physicians saw specialists most often, as expected.

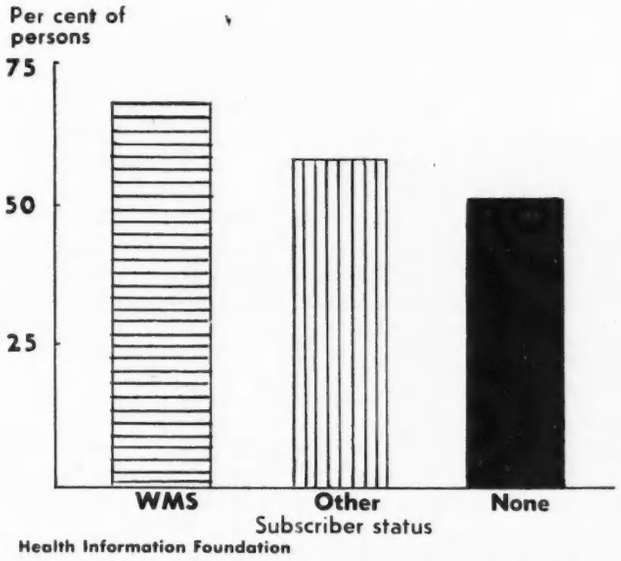

Fig. 3.—Patients having a regular doctor by subscriber status, Windsor, 1954.

Since WMS includes home calls as subscriber benefits, it might be thought that subscribers would tend to over-utilize and thus abuse this benefit. Windsor subscribers obtain about 13% of their physicians' services in their homes. Subscribers to other plans and the uninsured obtain 15% of their services in house calls.

PUBLIC'S EVALUATION OF WMS

As the Windsor study notes, people's evaluation of comprehensive physicians' care insurance helps answer the question of their willingness to pay for these benefits. It also indicates the intensity and direction of public opinion about health insurance.

Some kind of insurance for physicians' services is considered important by the majority of each group in Windsor. About 96% of Windsor subscribers, 90% of those in other plans, and 78% of the uninsured termed medical insurance "very important". "Insurance that covers all doctors' bills" was considered to be worth a specified additional charge to 80% of WMS subscribers, 75% of those in limited plans, and 67% of the uninsured.

While 84% of WMS subscribers termed themselves "highly satisfied" or "generally satisfied" with their plan, only about half of the subscribers to other plans felt this way about their coverage. In addition, over half of the uninsured group expressed interest in joining some plan that would cover doctors' bills. These attitudes toward comprehensive benefits were confirmed in Windsor by the substantial growth of WMS subsequent to the study year.

The three subscriber-status groups were asked if physicians' insurance should, in their opinion, continue to be handled privately or made the responsibility of the government. Among WMS subscribers, 24% favoured government control, while 60% preferred the present method of control. Among subscribers to limited plans, 34% favoured government control and 52% private control. Of the uninsured, 43% favoured government control and 31% preferred private means. The study conclusion: "WMS has the clear effect of reducing pressure for government intervention."

EFFECTS OF WMS ON MEDICAL PRACTICE

The medical profession of the Windsor metropolitan area consists of 211 physicians, 187 of whom are in full-time practice. There is no group practice in the area and few partnerships or full-time salaried arrangements.

Full-time physicians in Windsor—general practitioners and specialists combined—have an average patient load of about 115 patients per week. They work an average of 9.5 hours per day and earn an average annual net income of $13,762. General practitioners see more patients (126 a week), work longer hours (10.5 a day), and earn slightly less ($13,232 a year). Windsor physicians are, in the main, satisfied with their selection of Windsor as a place to practise and with the quality of medical care in the community.

For physicians in full-time practice, WMS subscribers constituted, on the average, about two-thirds of their total patient load and 60% of their total income during the study year. This proportion of patients is fairly evenly distributed among Windsor physicians. Eighty per cent of them had at least 50% WMS subscribers among their patients.

The frequent physician complaints about patients—that they wait too long before coming for care, "shop around" from doctor to doctor, demand unnecessary services or treatment, do not follow advice, etc.—are not considered large problems by most Windsor physicians. No more than 20% of Windsor physicians find any one of these very important. However, physicians with larger proportions of WMS subscribers as patients tend more often to consider "shopping around" and unnecessary house calls large problems; on the other hand, fewer are troubled by patients who wait too long before coming for care or disregard advice (see Fig. 4).

About 63% of Windsor physicians reported an increase in the proportion of their income derived from WMS over the few years prior to the study year. Of these, 40% were "very satisfied" with this increased dependence on the plan; 42% were "fairly satisfied"; 15% were "somewhat dissatisfied"; and 2% were "very dissatisfied".

Two principal reasons were given for the attitudes expressed. Those who were satisfied cited the steady,

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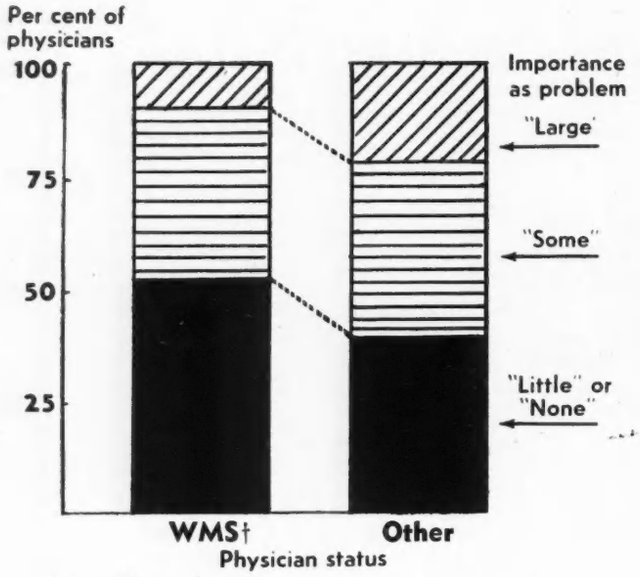

Fig. 4.—Evaluation* of patients' delay in initiating care, WMS† and other physicians, Windsor, 1954.

increased income that WMS had brought them. Those who were critical of the plan (including some who regarded themselves generally as satisfied) focused on the plan's fee schedule as "too low" or "too fixed".

Most physicians stated that WMS aided them in building and stabilizing their practices and enabling them to provide care without cost considerations, but not in regularizing their working hours. The effect of WMS on the quality of medical care was judged to be favourable by almost one-half the physicians and unfavourable by 15%. Similarly, the stabilizing influence of WMS on physician-patient relationships was regarded as helpful by 40% and not so by 15%.

Windsor physicians were almost unanimous in saying that WMS was doing a "very good job" in making medical care available to the public. About two-thirds agreed that WMS had also been generally in the best interests of physicians (another 29% felt that in some ways it had but in other ways it had not).

Of the physicians who are medical members of WMS, about two-thirds believe that doctors have an adequate voice in determining plan policy and that plan actions "usually agree" with their own point of view. Relative to the fee schedule itself, 27% are satisfied, 55% believe it requires "some change"; another 16% believe that major revision is needed. In general, there was less criticism of the procedures for revising fees. Most physicians are satisfied with the "taxing" procedures (by which physicians' claims are reviewed and adjusted, if excessive) and with the other aspects of their relation to the plan.

When asked their feeling about many different types of possible insurance benefits, Windsor physicians generally agreed: They favour comprehensive benefits for home, office, and hospital services, covering all costs except drugs and appliances, with the patient paying for the first visit or so and the physician being paid directly by the plan on a fee-for-service basis. With the exception of the suggested deductible feature, as an assumed control on "over-utilization", this payment-benefit pattern agrees with that applied by WMS. It is of interest, however, that without any deductible features WMS subscribers utilized one or two calls in no greater proportion than did those outside of WMS.

Cost of Processing Claims

About 96% of the physicians reported themselves as satisfied with the paperwork required of them. The only routine paperwork is the preparation of a monthly "claim card" for each WMS subscriber who visits the physician during the month. The card identifies the subscriber by name, address, and subscriber and group number; specifies the dates, number, and types of services rendered; and gives the fee for each service and the physician's diagnosis. The doctor may prepare duplicate cards for his own records, but the plan sends him a monthly statement listing his reported patients, his submitted fees for each patient, and fees allowed by the plan.

About 95% of the claim cards received by the plan are processed routinely. The remaining 5% require some consideration by the medical director or by a medical control committee. As a result of this review, an average reduction is made of about 3% of the total claims submitted by participating physicians.

In the sample month selected for analyzing costs, 47,750 claim cards were submitted, covering 71,998 services (1.51 services per claim card). Payments to physicians for the month were $290,267.30—$6.08 per claim card or $4.03 per service.

The cost of processing all claims received for the month, determined by allocating personnel time and other expenditures, was calculated to be $6,743.33. This amounted to 14 cents per claim card or 9 cents per service. Since the average claim is $6.08, the cost of processing amounts to 2.3% of the claim amount—far less than commonly believed.

Taken as a whole, this study of Windsor Medical Services indicates that comprehensive physicians' service insurance on a fee-for-service basis is feasible from the standpoint of doctor, patient, and prepayment plan alike.

ACCIDENT AND SICKNESS CLAIM FORMS

In the past six years the number of Canadians covered by group surgical insurance has doubled and the number with group medical insurance has tripled. Today over 2.8 million persons have group surgical cover and over 1.9 million have group medical cover provided by about 30 insurance companies. In addition, over 1.2 million Canadians have group weekly indemnity insurance.

Obviously, with more people insured there has been an increase in the number of requests made of physicians and surgeons for certifications upon which benefit payments are based. Doctors have accepted this "paper work" in the knowledge that they are thereby assisting patients in financing their medical care on the voluntary basis. However, many doctors have been aggravated by the variations in the wording and arrangements of the claim forms of the many insurance companies.

In 1954, The Canadian Life Insurance Officers Association, whose members provide the bulk of the group accident and sickness insurance in force in Canada, set up a committee to study the possibility of simplifying and standardizing accident and sickness claim forms. Shortly after the committee was named, both the Canadian Medical Association and the Ontario Medical Association approached the Life Officers Association independently, inviting the co-operation of life insurance companies in eliminating or at least reducing the many variations in their physicians' statements, and stating that this had become a problem of some concern to the medical profession.

The committee set as its desired objective that all life insurance companies transacting group accident and sickness insurance in Canada use forms asking the physician for the same information, preferably through the use of uniformly worded questions arranged in a uniform sequence.

After consultation with the medical associations, the committee developed model group insurance physicians' statements for weekly indemnity, supplementary weekly indemnity, surgical and medical benefits. In July 1955, these statements were submitted to the companies. The committee's objective was realized to the extent that life and other-than-life companies writing 80% of this insurance in Canada agreed to adopt the statements when their claim forms were next reprinted.

While the companies' old forms will undoubtedly turn up in physicians' offices from time to time, the standard statements are coming into more extensive use. Generally the life insurance companies are hopeful that in the near future doctors will be reaping the full benefit of the efforts that have been made to simplify group claim forms.

MISCELLANY

EMOTIONALLY DISTURBED CHILDREN

A NEW APPROACH IN B.C.

The following is an excerpt from the British Columbia Public Welfare Services report for 1956:

> "There is always a certain number of children in care, of pre-school age, who are sick and disturbed to the point where they can be readily recognized as potential candidates for institutional care of one kind or another. They are too upset to respond to foster-home care, and no attempt at treatment can be made by the field staff with the limited amount of supervision time available to them. Untreated, these are children who, as adolescents and young adults, break as psychotics and enter a mental hospital, or because of their neurosis or character disorder break laws or live crippled, unhappy lives in communities. When either occurs, the cost in terms of custodial care they will need throughout their lives—to say nothing of the loss in human resources—mounts to a staggering figure. Treated properly when treatment could still be of help, many would be saved for useful, constructive citizenship. Treatment facilities of this nature are most urgently needed in British Columbia."

RUBY MCKAY,
Superintendent of Child Welfare.

Over a period of many years a group of professional and well-informed lay people in Vancouver has recognized that this need exists not only for children "in care", but equally for those from well-established families in all income groups. Based on intensive research and study, a joint committee of the Vancouver Community Chest and the Canadian Association of Social Workers, B.C. Mainland Branch, evolved a plan for what they considered to be the most appropriate setting for the treatment of such children. As a result of this planning the "Children's Foundation" was incorporated in January 1957, to establish a residential treatment centre for emotionally disturbed children.

The program is designed for the child aged six to twelve, as this is the age group most likely to respond to treatment. The objective is a controlled living situation in which the child, through intensive individual treatment, will learn to live and work with others, to have confidence in them and in himself. The child's placement in the home will be only one stage of the treatment, which, in total, will include work with the child, parents and community before, during and following such placement. The main purpose is then the return of a happier child to a healthier community.

This program will, it is hoped, have the added value of providing training and research opportunities to the professions concerned.

The atmosphere of the home will be as close to that of a large family as possible. Therefore, accommodation will be limited to fifteen children at any one time. The location will be near an elementary school in a residential area. Specially trained visiting teachers will be part of the treatment team for those children who are not considered well enough to attend public school. The children will be helped to be aware of the purpose of their stay in the home.

It is estimated that the length of stay in the home will vary from six months to two years, according to the therapeutic needs of each child. A follow-up after discharge is planned so that after the initial period the staff will have under treatment more than the fifteen children in residence.

In order to carry out such a program a qualified staff is essential. The Foundation has planned for a staff both adequate in numbers and trained in the skills necessary to understand and treat troubled children. The personnel will include the following: psychiatrist, psychologist, case worker, group worker, teacher and house parents, all with an orientation of modern dynamic concepts.

A thorough diagnostic and prognostic assessment will determine whether or not the individual child can be served in this home. The clinical director, i.e., psychiatrist, as head of the treatment team will be the unifying person who takes all factors into account in the diagnostic admission process.

The Children's Foundation relies on public understanding and support. Further information may be obtained through writing to the Children's Foundation, 1625 West Eighth Avenue, Vancouver, B.C.

ELDA LINDENFELD, M.D.

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HOUSING APPLICATION FORM

91st Annual Meeting, C.M.A. — Halifax, June 16 - 20, 1958

Dr. M. R. Macdonald,
Chairman, Committee on Housing, C.M.A.
30 Armshore Drive,
Armdale, Halifax, N.S.

Please reserve the following accommodation:

..... Double room (bath or shower) twin beds ..... double bed.....

..... Room for ..... person(s) (bath or shower)

..... Motel Unit for ..... persons (bath or shower)

..... Tourist Home for ..... persons

In view of the large attendance expected, the hotels have few, if any, single rooms available. It might be to your advantage to share a room with another member. Please mention below the name of the person with whom you would like to share your accommodation; otherwise assignment will be made by the Housing Committee.

Names of persons who will occupy the accommodation requested above:

NAMES (Dr. and Mrs.) ....

ADDRESSES ....

I (we) will arrive in Halifax on June..... at ..... a.m. p.m.

I (we) will depart from Halifax on June ..... at ..... a.m. p.m.

Travelling by: Automobile..... Train..... Air..... Bus.....

Please check choice of accommodation:	First	Second	Third
Hotel	.....	.....	.....
Motel	.....	.....	.....
Tourist Home	.....	.....	.....

NAME .....

ADDRESS .....

.....

TELEPHONE No.....

THIS WILL CONSTITUTE YOUR ADVANCE REGISTRATION FOR THE MEETING

Association Notes

DOMINION INCOME TAX RETURNS BY MEMBERS OF THE MEDICAL PROFESSION

[*We publish herewith the text of a memorandum approved by the Department of National Revenue for the guidance of doctors making income tax returns relative to the year 1957.*]

As a matter of guidance to the medical profession and to bring about a greater uniformity in the data to be furnished to the Taxation Division of the Department of National Revenue in the annual Income Tax Returns to be filed, the following matters are set out:

Individuals whose income—(a) is derived from carrying on a business or profession (other than farming); (b) is derived from investments; or (c) is more than 25% derived from sources other than salary or wages, are required to pay their estimated tax by quarterly instalments during such year. Each payment must be sent in with Income Tax Instalment Remittance Form T7C. Any balance of Income Tax due is payable on or before the 30th April of the succeeding year, plus interest where applicable.

Doctors who pay salaries or wages to employees are required to deduct tax therefrom in accordance with the Table of Tax Deductions obtainable from District Taxation Offices. Each employee should complete and file one copy of form TD1 with his employer (a) at commencement of employment and (b) within seven days of any change in circumstances affecting his personal exemptions. If Form TD1 is not filed, tax deductions must be made as though the employee were a single person. Tax deductions withheld from salaries or wages must be sent to the local District Taxation Office not later than the 15th day of the following month accompanied by Tax Deduction Remittance Form TD7A.

The following timetable indicates the returns required:

A. Doctors NOT receiving salaries amounting to ¾ of income:

Date due	*Forms to be used*
March 31	Form T7C
April 30	Form T1 General
June 30	Form T7C
September 30	Form T7C
December 31	Form T7C

B. Doctors receiving salaries amounting to ¾ or more of income:

Date due	*Forms to be used*
April 30	Form T1 General (Note. Doctors whose earned income consists solely of salary and whose investment income is not over $2,500 may use Form T1 Short unless they claim a capital cost allowance or a foreign tax credit.)

C. Doctors who pay salaries to their own employees:

Date due	*Forms to be used*
15th of each month	Form TD7A
February 28	Form T4 Summary and Supplementary

Details of the total salaries or wages paid to employees and the tax deducted therefrom must be forwarded to the local District Taxation Office on Forms T4 Summary and T4 Supplementary not later than the last day of February in each year.

INCOME

Under the provisions of the Income Tax Act a doctor is required to maintain an accurate record of all income received both as fees from his profession and by way of investment income. The record should be clear and capable of being readily checked against the return filed. It may be maintained on cards or in books kept for the purpose. Such records must not be destroyed until written permission for their disposal is obtained from the Minister of National Revenue.

EXPENSES

Under the heading of expenses, the following accounts should be maintained and records supported by vouchers kept available for checking purposes.

(a) Medical, surgical and like supplies.

(b) Salaries or wages paid to professional assistants, nurse, office help, bookkeeper. (It is to be noted that the Income Tax Act does not allow as a deduction a salary paid by a husband to a wife or vice versa. Such amount, if paid, is to be added back to the income.)

(c) Telephone expenses (long-distance charges on business calls and service charges for business telephones listed in the doctor's name, fees for telephone answering services).

(d) Assistants' fees; the names and addresses of the assistants to whom fees are paid should be furnished. This information is to be given each year on Income Tax form known as Form T4, obtainable from your District Income Tax Office.

(e) Rentals paid. The name and address of the owner (preferably) or agent of the rented premises should be furnished (see (i)).

(f) Postage and stationery.

(g) Depreciation or capital cost allowance as it is referred to in the Income Tax Act; a description of the treatment of depreciation may be found on page 4 of the Income Tax Return Form T1 General under Part XI Method, and the 1957 T1 General Information sheet.

The method of computing depreciation for tax purposes is the same as that used last year and you should have no difficulty if you have a copy of last year's return available.

Simply carry forward the balance remaining in each class after deducting last year's allowance. Add to this figure the cost of any new equipment purchased and deduct the proceeds from any disposal of property in each class. The rate you wish to use not exceeding the maximum rate (see below) is applied to this new balance for each class to obtain the depreciation you may claim this year.

The maximum rates for the classes of equipment used by doctors follow:

Capital item	*Class*	*Annual maximum depreciation*
Medical equipment:		
(a) Instruments costing over $50 each and medical apparatus of every type	8	20%
(b) Instruments under $50 each	12	100%
Office furniture and equipment	8	20%
Motor car	10	30%
Buildings of frame construction	6	10%
Buildings of brick construction	3	5%

Where a doctor practises from a house which he owns and resides in, the allowance may be claimed as above on a portion of the cost of the residence, excluding land. For example, if the residence were a brick building costing $12,000 and one-third of the space were used for the office, the doctor would use $4,000 as the business portion of the cost and apply the building rate of 5% to determine the maximum depreciation allowable in the first year.

For further information on the subject you may refer to the Income Tax Regulations or you may consult your District Taxation Office.

(h) Automobile expense (one car). This amount will include cost of licence, oil, gasoline, grease, insurance, garage charges and repairs.

The capital cost allowance is restricted to the car used in professional practice and does not apply to cars for personal use.

Only that part of the total automobile expense incurred in earning the income from the practice may be claimed as an expense and therefore the total expense must be reduced by the portion applicable to your personal use.

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(i) Proportional expenses of doctors practising from their residence.
  (a) owned by the doctor: where a doctor practises from a house which he owns and as well resides in, a proportionate allowance of house expenses will be given for the study, laboratory, office and waiting room space, on the basis that this space bears to the total space of the residence. The charges cover taxes, light, heat, insurance, repairs, capital cost allowance, and interest on mortgage (name and address of mortgagee to be stated).
  (b) rented by the doctor: only the rent and other expenses borne by the doctor such as heat and light will be apportioned inasmuch as the owner takes care of other expenses.

The doctor should be prepared to demonstrate, if called upon to do so, that his apportionment of any particular item is in accordance with the facts relative to that item.

(j) Sundry expenses. These should cover only small items not otherwise classified, for example, laundry, malpractice insurance, etc. The expenses charged to this account should be capable of analysis and supported by records.

Claims for charitable donations should be made in the space provided for this item on the Income Tax forms and should not be included in the professional expenses. Such claims are allowable as a deduction from income up to 10% of the net income upon submission of receipts to your District Taxation Office.

For 1957, donations made in 1956 that were in excess of the maximum may be claimed, but the total allowed for those so carried forward and the 1957 donations will be limited to 10% of net income.

The annual dues paid to governing bodies under which authority to practise is issued and membership association fees, to be recorded on the return, will be admitted as a charge. Initiation fees and the cost of attending postgraduate courses will not be allowed.

(k) Interest. Interest paid on borrowed money may or may not be charged as an expense according to the use made of the borrowed money. For example, if it was used to acquire an interest in a partnership or to buy professional equipment, the interest paid may be claimed as an expense in computing professional income, while if it was used to acquire securities or real property, the interest paid may be claimed as an expense in computing the income received from the securities or real property. On the other hand, interest paid on money borrowed for personal use may not be claimed as a deduction from any kind of income.

(l) Business tax will be allowed as an expense, but Dominion, Provincial or Municipal income tax will not be allowed.

(m) If no claim is made for charitable donations, association fees or medical expenses, a deduction of $100 is allowable.

CONVENTION EXPENSES

Under Section 11(i)(ia) of the Income Tax Act, convention expenses are allowable to an individual carrying on a business or practising a profession, but the allowance is restricted to the expense of attending no more than two conventions in a taxation year. Furthermore, the taxpayer's attendance at the convention must have been for business or professional reasons. There are no geographical restrictions and the convention, therefore, need not necessarily have been held in Canada.

As heretofore, the expenses to be allowed must be reasonable, and the taxpayer should show:

(1) The dates on or between which the convention was held, and the location thereof;

(2) The number of days he was present at the convention, supported by certificate of attendance from the sponsoring organization; and

(3) The expenses incurred, segregating
  (a) transportation expenses
  (b) meals, and
  (c) hotel expenses, for which at least vouchers should be obtained and kept available for inspection.

All expenses of a personal nature, including those attributable to the fact that the taxpayer's wife (or husband as the case may be) accompanied him to the convention, must be excluded from the foregoing.

No expenses for attending a convention are allowable as a deduction from salary income, since such a deduction is prohibited by Section 5 of the Act.

REGISTERED RETIREMENT SAVINGS PLANS

The amount that is deductible in respect of contributions to a retirement savings plan is limited

(a) in the case of an employee receiving a salary who is covered by an employer-employee pension plan to the lesser of $1,500 or 10% of his earned income; and

(b) in other cases to the lesser of $2,500 or 10% of his earned income. "Earned income" usually consists of income received as salary (before any pension deductions) or income from carrying on a business or profession, plus net rental income.

The amounts deductible are those paid in 1957 and within 60 days after the end of the year. A payment made in January or February of 1958 cannot be claimed in 1958 if it could have been deducted in 1957.

Individuals enquiring whether a proposed or existing plan is acceptable should usually request that information from the corporation offering the plan as it will normally be the corporation's responsibility to explain the plan and get it registered.

Doctors who have applied for membership in the Canadian Medical Retirement Savings Plan prior to December 31, 1957, may be assured that their names are registered as participants in a registered retirement savings plan and that their contributions are deductible for the taxation year 1957. The closing date of February 9, 1958, has been established by arrangement with the Bank of Montreal for C.M.R.S.P. contributions applicable to 1957. Certificates showing the amount of contributions will be mailed to C.M.R.S.P. members in March 1958 to support claims made for deductions in their 1957 income tax returns.

Applications for membership in C.M.R.S.P. received during the current year will entitle participants to tax deferment for 1958.

PROFESSIONAL MEN UNDER SALARY CONTRACT

The Income Tax Act provides that income from an office or employment is liable to tax without deductions of any kind except such as are specifically provided for in the Act. The allowable deductions include the employee's contributions to a pension fund, alimony, travelling expenses, annual professional membership dues, office rent, salary to an assistant or substitute, supplies consumed directly in the performance of the duties of employment and amounts paid into a retirement savings plan.

Section 11 (10) (a) of the Income Tax Act permits the deduction from income of an office or employment of annual professional membership dues only if their payment was "necessary to maintain a professional status recognized by statute".

The annual registration fee of the Provincial medical licensing authority would be allowable if paid by the doctor himself.

Certain conditions are attached to the allowance of the expenses, and without trying to recite the exact provisions of the law, it may be said the main points are that:

(a) The expenses must have been incurred in the performance of the duties of the office or employment.

(b) The employee is required, under the contract of employment, to pay the expenses.

(c) To claim travelling expenses the employee must be ordinarily required to carry on the duties of his employment away from his employer's place of business. Travelling between the doctor's home and his office is not included.

Where travelling expenses are allowable under these provisions, depreciation may be claimed on the automobile used for this purpose, but no other claim for depreciation may be made.

INCOME FROM A PARTNERSHIP

Additional expenses incurred by a partner, but not charged to the partnership, may be claimed as a deduction from the partner's share of income. However, the partner must be in a position to substantiate these expenses, to show why they were not charged directly to the partnership and that they were necessarily laid out to earn the partnership income.

THE 91ST ANNUAL MEETING

EXECUTIVE COMMITTEE

The Executive Committee of the C.M.A. will meet in Charlottetown, P.E.I., on June 13 and 14, 1958. It is hoped that other members attending the annual meeting in Halifax will take advantage of the relative proximity of Prince Edward Island to pay a visit to this charming land known as the "Garden of the Gulf".

The charm of this crescent-shaped island impressed our forefathers so much that Jacques Cartier described it as "low and beautiful land". Champlain's Ile Saint-Jean changed its name to Prince Edward Island in 1798 in honour of the father of Queen Victoria. This tiny province, which was the birthplace of Confederation, is only 140 miles long by four to 40 miles in width. Its greatest elevation is 500 feet, and its northern shore facing the Gulf of St. Lawrence is lined with beautiful sand beaches which make it an ideal tourist resort in summertime. The mean temperature of the Island in July is said to be 65°, so that the heat wave which seems to characterize the meeting each year should not affect our members this time. Golf addicts will be amply rewarded by a visit to the Island after they have played the Cavendish course or the Green Gables Golf Links, both of which have an excellent reputation in the world of sports. Boating, motoring and horseback riding also offer pleasurable moments on the Island. Even if the annual meeting falls in the off-season for the famous Malpeque oysters, the amateurs of seafood will delight in fresh lobsters which are plentiful in the region.

Prince Edward Island is within easy reach of the mainland through excellent air communications and also through the services of the *Abegweit*, the largest car ferry of her type in the world—named after the Micmac name for the Island ("the home cradled on the waves")—and her sister ship the *Prince Edward Island*. These two vessels have a capacity for 150 automobiles and 19 railway cars. The Canadian National Railways run a line from Sackville, N.B., to Cape Tormentine on the straits of Northumberland. The ferry-boats link Cape Tormentine with Port Borden on the Island.

MEDICAL SOCIETIES

MONTREAL PHYSIOLOGICAL SOCIETY

On November 1, 1957, a combined meeting of the Fellows' Society of the Montreal Neurological Institute and the Montreal Physiological Society was held in the amphitheatre of the Montreal Neurological Institute, in memory of the 100th birthday of Sir Charles Sherrington. His son, C. E. R. Sherrington, spoke on "The Man in Retrospect"—namely his father. Sir Charles Sherrington was chairman of the Department of Physiology from 1913 to 1935, and a leader in the field of neurophysiology. In his talk, Mr. Sherrington emphasized the human side of his father's life and allowed us to hear interesting and little known aspects of the life of this great physiologist.

The Montreal Physiological Society came into being well over 20 years ago and since then has held evening scientific sessions monthly, throughout the academic season. After much discussion, the Constitution of the Society was changed at the last Annual General Meeting to allow a modification in the type of meetings. The Program Committee had planned two all-day scientific sessions in place of evening meetings, and the first was held on Friday, November 29, from 9 a.m. to 5 p.m. at the Montreal General Hospital. The program included the *Merck Lecture of McGill University*, given by *Dr. James A. F. Stevenson*, Professor of Physiology, University of Western Ontario, on "Hunger and Thirst".

Drs. J. Genest, E. Koiw, W. Nowaczynski and G. Leboeuf of the Clinical Research Department, Hôtel-Dieu Hospital, determined urinary aldosterone in 33 normal subjects, by the new chemical method (*Canad. J. Biochem. & Physiol.*, 35: 425, 1957). The mean excretion was 3.6 micrograms per day with a range of 1 to 9.5 mcg. per day; 46 determinations on 34 patients with essential, renal and malignant hypertension showed a mean excretion twice the normal and 50 to 60% of these patients had urinary aldosterone levels higher than normal or in the higher limits of normal. In addition 17 determinations were performed in eight patients with coarctation of the aorta, Cushing's disease, phæochromocytoma and primary aldosteronism. In some cases, the same patients were re-studied following surgery. Urinary aldosterone excretion was determined in a normal subject on usual activities and self-selected diet for two consecutive days in June 1956 and for nine consecutive days in November 1956. It remained fairly constant between 1.3 to 6.5 μg. per day despite variations in urinary sodium from 66 to 386 mEq. per day. On the other hand, a patient with asymptomatic benign essential hypertension was studied for five consecutive days and the aldosterone excretion was 7, 15.7, 3.6, 9.3 and 14 μg. per day with a urinary sodium between 150 and 170 mEq. per day. In all patients and normal subjects on a self-selected diet, no correlation could be observed between aldosterone excretion and sodium intake (as reflected by the urinary sodium which varied between 50 and 400 mEq. per day) or urinary Na/K or K/Na ratios. These findings bring additional evidence for a mineralocorticoid disturbance of the adrenals in human hypertension. They also show that sodium intake has little effect on aldosterone excretion unless it is below 40 mEq. per day.

Dr. R. Hobkirk of the Department of Biochemistry, McGill University, reported studies at Glasgow of excretion of 11-deoxy, 17-ketosteroids after pituitary destruction in patients with breast cancer. No obvious difference in tumour remission appeared to exist between groups of patients treated by adrenalectomy on the one hand and attempted pituitary destruction on the other (radon, yttrium-90). No certain correlation was found between tumour remission and steroid excretion following attempted ablation, although measurement of individual 17-ketosteroids might be a useful indication of adrenocortical activity. On occasion, excretion of 11-desoxy, 17-ketosteroids was still low after apparently complete surgical ablation. Therefore, when steroid excretion continues rather high, as after treatment of the pituitary with radioactivity, incomplete ablation is suggested.

Drs. G. Weber and A. Cantero of the Montreal Cancer Institute, Notre-Dame Hospital, had previously shown that the liver phospholipid content of the Novikoff hepatoma in rats was only 32% of that of the normal liver. This seemed characteristic of neoplastic fast-growing liver, since no such decrease was seen in the fast-growing regenerating liver. This observation has now been verified by the isotope method using P^{32}. The decrease in phospholipids in the Novikoff hepatoma may be the result of decreased synthesis of this compound.

Penicillamine (β, β^1-dimethylcysteine) was introduced into clinical medicine as a treatment for hepatolenticular degeneration. *Dr. J. E. Boulding* of the Allan Memorial Institute of Psychiatry reported on the use of this new, orally effective chelating agent in six cases of metal intoxication. An 18-year-old male with hepatolenticular degeneration, a helpless, bedridden invalid, was treated with penicillamine for 12 months; there was sustained and marked copper diuresis and a dramatic and continuous clinical improvement. Hepatolenticular degeneration in a 24-year-old

female, disabled by a severe intention tremor, was treated with penicillamine for one month; satisfactory copper diuresis occurred. A 40-year-old male, exposed to lead vapours, had a higher number of stippled red blood cells than permitted by industrial hygiene regulations and was removed from exposure; urinary lead rose to high levels when the patient was given penicillamine for three days. A 27-year-old female, exposed to lead vapours for six years, was admitted to hospital with peripheral neuritis, abdominal colic, and marked fluctuations in mood. For one month she was given the conventional regimen for lead poisoning with no benefit; two weeks' treatment with penicillamine led to marked lead diuresis and recovery. A man with transfusion hæmosiderosis was given penicillamine for three days; urinary iron excreted in 24 hours rose slightly on the third day. Lastly, in a woman with hæmachromatosis given penicillamine for 12 days, urinary iron showed no change during drug administration.

Drs. C. Sinnott and D. J. MacIntosh, Montreal General Hospital, measured simultaneously ventilation and alveolar CO_2 tension in over 100 persons during exercise of various grades of severity. In each instance respiratory drive was quantitated in terms of oxygen ventilatory equivalents. CO_2 tension was not a significant factor in determining physiological respiratory drive during exercise, but passively followed the ventilation and was itself determined primarily by the lead of respiratory drive. The role of CO_2 in the control of ventilation may have to be reconsidered.

Dr. J. Langman of the Department of Anatomy, McGill University, reported on changes in serum protein pattern during pregnancy. Normally, alpha and beta globulins tend to decrease somewhat during the course of pregnancy, while gamma globulins show an equivalent increase. In a pathological pregnancy in rabbits and in women (in abortion or congenital abnormality) the changes in the protein pattern differ considerably and may be specific.

Drs. T. L. Sourkes, B. D. Drujan, R. B. Sloane and G. Curtis of the Allan Memorial Institute of Psychiatry, McGill University, measured by the lutin fluorescence method the rate of excretion of pyrocatecholamines (adrenaline, noradrenaline and hydroxytyramine) in morning urine of subjects receiving electroshock therapy (EST). Subjects with a low excretion rate tend to improve with EST, whereas "high excretors" tend not to benefit. Predictability of improvement from the chemical data is about 75%, based on studies of 37 subjects examined on 97 treatment-days. No relation between excretion rate of total PCA and age of patient, weight or sex was found. In recent studies adrenaline has been estimated separately from the "noradrenaline-like substances"; with this modification, results indicate that EST causes a relative increase in excretion rate of adrenaline at a time of day when the rate is normally (i.e. no treatment) declining. The effect on "noradrenaline" excretion is quite variable.

Recent studies of peripheral circulation in cats by Renkin, and in man by Freis, support the hypothesis that the peripheral circulation is composed of flow through two unequal and parallel systems. *Drs. W. E. Wilson and M. A. Entin* of the Queen Mary Veterans' Hospital have reinvestigated this by modifying the constant rate injection technique of Andres and Zierler, and the Freis rapid injection method. Indicator dilution curves were obtained by intra-arterial injection and venous sampling in a series of 34 dogs. The indicators were T-1824 and Cr^{51} tagged red cells. The shape of the late downslope curves by the two methods confirmed existence of a double circulation.

Repetitive stimulation of the amygdala evokes recruiting responses in the hippocampus and creates a prolonged state of raised excitation of hippocampal neurons. This can be demonstrated by the presence of potentiation of hippocampal responses to single electrical shocks applied to the amygdala after the end of a period of repetitive amygdaloid stimulation. If stimulation is intense enough, excitation of hippocampal neurons may lead to seizure discharge. *Dr. P. Gloor* of the Montreal Neurological Institute reported on a laminar analysis of these phenomena with 12 μ Pt-wire microelectrodes. This showed that the build-up of the excitatory state responsible for recruitment and potentiation occurs in the layer of apical dendrites of the hippocampal pyramidal neurons and of the granule cells of the dentate gyrus. This build-up of excitation appears to be a function of specific properties of axodendritic synaptic junctions. During seizure discharge the main location of the excitatory process shifts from the apical dendrites to the basal area around the soma, and this seems to be due to afferent bombardment from the granule cells of the dentate gyrus discharging over the mossy fibres of the hippocampus.

Drs. L. Jarry and H. K. Uhthoff, of the Department of Orthopædics, Verdun General Hospital, and Department of Physiology, University of Montreal, described a procedure applicable in open reduction of transverse fractures of long bone diaphyses by using a new so-called "petal" technique. By increasing the contact area of the fragments, especially with the surrounding soft tissue, by promoting the anchoring processes near the fracture site, and by biological changes in compact bone, fracture consolidation was accelerated, as shown by stability tests, radiological examinations and by histological studies.

Dr. P. R. Bromage, of the Department of Anæsthesia, Royal Victoria Hospital, discussed alterations of the phrenic reflex in thoracic spinal blockage. Fifty-two patients undergoing thoracotomy were anæsthetized by lumbar epidural blockade in combination with light endotracheal anæsthesia (Pentothal, N_2O and O_2). Epidural analgesia was induced with 1.5% Xylocaine and maintained through a vinyl plastic catheter inserted in any convenient interspinous space between T10 and L2. The upper limit of analgesia was carried to a level between C6 and T4, so that the phrenic motor and sensory roots were not blocked, and normal spontaneous diaphragmatic movement could take place. Apnœa was induced by hyperventilation. Under these circumstances the peripheral portion of the diaphragm is insensitive, but the central portion (innervated by the third, fourth and fifth cervical nerves) retains its sensation and is free to react to direct stimulation. However, direct stimulation of the central portion of the diaphragm during operation failed to produce a coordinated contraction, although full contraction resulted if the phrenic nerve was stimulated. Control cases under light general anæsthesia without epidural block had a vigorous contractile response to stimulation of the central portion of the diaphragm. The following hypothesis was presented to explain the above observations: phrenic reflex activity is dependent upon summation of a number of different afferent stimuli which can be envisaged as comprising a neuronal "pool". Depletion of part of the total afferent neuronal "pool" leads to depression of the phrenic spinal reflex, since the motor threshold cannot be reached. The neuronal "pool" is normally fed by contributions from the upper sympathetic rami carrying impulses from the lungs and thoracic wall, together with cerebrospinal afferents from the thoracic cage and parietal pleura. When these afferent impulses are eliminated by high spinal blockade, the remaining afferent pathways in the phrenic nerve cannot carry an adequate volume of stimuli to produce a motor response.

In addition, a number of studies of a more fundamental nature were presented. *Drs. C. von Seemann, C. I. Chapel and G. A. Grant* presented data on new synthetic antitussive agents. *Dr. A. Beaulnes* spoke on the effect of glucose, calcium and magnesium on atrial arrhythmias induced in the isolated rabbit atria. O-methylation of catechol acids by rat liver and kidney preparations was discussed by *Drs. J. Pellerin and A. D'Iorio;* and studies on the mechanism of insulin sensitization to anaphylactoid inflammation were reported by *Dr. V. W. Adamkiewicz. Drs. P. Sacra and J. D. McColl* reported on modification of neurotoxicity produced by β, β^1 iminodipropio-nitrile. *Drs. G. de Lamirande, G. Weber and A. Cantero* presented data on the effect of x-irradiation on liver enzymes involved in nucleic acid catabolism in normal and hypophysectomized rats. The pathogenesis of dextran œdema was described by *Drs. G. Jasmin and P. Bois;* the possible role of sex hormones and adrenocortical hormones in control of gastric secretion was presented by *Dr. D. R. Wood;* and factors affecting the survival of platelets in stored blood were reviewed by *Drs. E. Wilson and B. Bain.*

A. H. NEUFELD

INTERNATIONAL COLLEGE OF SURGEONS

The 11th biennial International Congress of the International College of Surgeons will be held in conjunction with the 23rd annual Congress of the

United States and Canadian Sections (North American Federation) in Los Angeles, March 9-14. An innovation will be a surgical emergencies panel to which members of the American Academy of General Practice are invited.

The scientific program to be presented in the Ambassador Hotel will consist of general assembly and sectional meeting presentations of papers, panels and symposia. A wide range of subjects will be presented in the general sessions, with particular emphasis upon the latest world developments in surgery. The impact of sputnik upon American medicine will be discussed. There will be 11 sectional programs. Surgical films will be shown. At the annual convocation and induction of new members into the College, which will be the concluding event, Dr. Raymond B. Allen, chancellor of the University of California, Los Angeles, will be the speaker. The annual dinner in the Palladium on March 12 will be entertained by Bob Hope, Miss Dorothy Kirsten and other theatrical stars.

Additional information may be had by writing to Dr. Ross T. McIntire, executive director, International College of Surgeons, 1516 Lake Shore Drive, Chicago 10.

AMERICAN MEDICAL ASSOCIATION

A recent Secretary's Letter from the American Medical Association reminds us that the general managership of our sister association has changed hands. On New Year's day, Dr. F. J. L. Blasingame, formerly a busy surgeon in Wharton, Texas, abandoned the scalpel for the pen and succeeded Dr. George Lull as general manager. Dr. George Lull worked for 12 years as secretary and general manager of the A.M.A., and was honoured by 205 of its employees on his retirement as general manager on Monday, December 30, 1957. Good wishes will be extended to him in his retirement, and also to his successor, already well-known in A.M.A. circles for his services on the Board of Trustees.

THE ASSOCIATION OF OPHTHALMOLOGISTS OF THE PROVINCE OF QUEBEC

Legally incorporated by the Provincial Legislature, the Association of Ophthalmologists of the Province of Quebec invites all Quebec doctors who specialize in ophthalmology to join. This Association is officially approved by the College of Physicians and Surgeons of the Province of Quebec.

The main objectives of the Association are to maintain high scientific standards for ophthalmologists, so as to give better service to the community and safeguard the rights of its members. Specifically, the Association intends to cover all the fields within its jurisdiction, and at the same time deserve the active sympathy and support of all existing medical organizations.

The Executive Council of the Association is as follows: President, Dr. René Charbonneau, Montreal; Vice-president, Dr. John Nicholls, Montreal; Secretary-Treasurer, Dr. Michel Mathieu, Montreal; Councillors, Dr. Jules Brault, Montreal, Dr. K. B. Johnston, Montreal, Dr. J. Arthur Fafard, Levis, Dr. Emile Pelletier, Quebec, Dr. François Badeaux, Montreal, Dr. J. Rolland Viger, Montreal, Dr. Jean Lacerte, Quebec.

LETTERS TO THE EDITOR

TONSILLECTOMY AND THE RISK OF POLIOMYELITIS

To the Editor:

I read the article on "Tonsillectomy and the Risk of Poliomyelitis" (this Journal, September 15, 1957) with interest. The household contact controls used in this survey do not appear, however, to be valid controls in the usually accepted sense.

The authors have compared two groups: (a) those with clinical poliomyelitis (i.e. non-immunes) and (b) those without clinical poliomyelitis. It is clear that whereas the first group was homogeneous with respect to its immunity state to poliomyelitis virus, the "control group" was a heterogeneous one composed of individuals who were immune to poliomyelitis or who were non-immune and had subclinical infection or who were non-immune but were not infected for some reason. The two groups were so dissimilar that they cannot be compared.

To determine whether tonsillectomy actually predisposes to clinical poliomyelitis, a more carefully controlled survey than the one under discussion would be needed and would, of necessity, include tests to indicate the immunity status of the controls and the incidence of subclinical poliomyelitis amongst them. An alternative approach to the problem is the longitudinal study of a population—an approach now rendered almost impossible by the widespread application of vaccination against poliomyelitis.

R. J. FALLON, B.Sc., M.D.

Bacteriology Department,
Western Infirmary,
Glasgow, W.1, Scotland,
December 27, 1957.

ABSTRACTS *from current literature*

MEDICINE

Pulmonary Disability as a Symptom of Amyotrophic Lateral Sclerosis.

R. D. MILLER: *Proc. Staff Meet. Mayo Clin.*, 32: 436, 1957.

Amyotrophic lateral sclerosis frequently affects the muscles of respiration. In particular, the terminal phases of this disease usually are characterized by aspiration pneumonitis and respiratory failure. Occasionally, however, a patient with amyotrophic lateral sclerosis may complain of exertional dyspnœa early in the course of the disease, before muscular atrophy and fasciculation in the usual groups of muscles becomes evident. In these unusual instances, if the breath sounds or thoracic excursions are diminished

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one might be led to make a diagnosis of pulmonary emphysema. Occasionally an erroneous diagnosis of cardiac failure is entertained.

When there is no positive sign of primary cardiac or pulmonary disease, the possibility of weak respiratory muscles as the cause of dyspnœa must be kept in mind. The diagnosis of amyotrophic lateral sclerosis must be considered initially on the basis of clinical information, although neurologic consultation often is necessary to corroborate this impression. Studies of pulmonary function may be of diagnostic aid. Certain abnormalities of pulmonary function may be misleading, however, since they superficially resemble changes in emphysema. These abnormalities are subnormal vital capacity, subnormal maximal breathing capacity and a high ratio of residual volume to total capacity of the lungs. The oxygen saturation of arterial blood also may be low. Some other features of abnormal pulmonary function may distinguish neuromuscular respiratory disorders from those of emphysema. These include reduced value for total pulmonary capacity, absence of significant increase of residual volume or functional residual capacity, and absence of expiratory slowing. Inspection of the spirogram made during a "rapid vital capacity" effort reveals a relatively rapid and constant expiratory rate resembling that often seen in patients with respiratory weakness following poliomyelitis. The curve has a constant relatively steep slope unlike that seen in emphysema, in which there is progressive expiratory slowing.

Paralysis of the pharyngeal and laryngeal muscles leads to aspiration of oral contents with resulting pneumonitis and subsequent fibrosis. This accentuates the pulmonary disability. S. J. SHANE

The Clinical Syndrome of Amyotrophic Lateral Sclerosis.

W. MULDER: *Proc. Staff Meet. Mayo Clin.*, 32: 427, 1957.

The diagnosis of amyotrophic lateral sclerosis is not difficult when the disease is far-advanced. The patient, usually a man in his forties or fifties, presents a clinical picture of widespread asymmetric steadily progressive muscular weakness with atrophy and fasciculations and associated hyperreflexia and spasticity in the remaining musculature. Muscles controlling eye movements are not involved, and impairment of bladder sphincters is infrequent. Although cramping muscular pains are a frequent complaint, objective sensory impairment is not a part of the clinical picture. The electromyogram is usually sufficient in such a patient to confirm the diagnosis. Such common neurologic diseases as multiple sclerosis, myasthenia gravis, or parkinsonism should be considered, but they rarely offer a real diagnostic problem. When the muscular weakness, atrophy, and fasciculations are limited to only a few segments, one must consider the possibility of a compression syndrome of the spinal cord. The most common causes of this syndrome are tumours, hypertrophic ridging of the cervical spine, or protruding disks in the upper cervical cord. These or similar lesions causing compression of the anterior spinal cord may give rise to spasticity, localized atrophy, weakness, and fasciculations, but sometimes few, if any, sensory findings. The differential diagnosis in these patients will often be aided by a carefully performed myelogram which should include the entire spinal cord to the level of the foramen magnum. Syringomyelia and syringobulbia may give rise to similar localized areas of muscular weakness with spasticity. The areas of muscular weakness are usually spread over more myotomes in patients with amyotrophic lateral sclerosis and the onset is usually more insidious. The diagnosis is dependent on the recognition of the characteristic sensory loss, which may at times be difficult to ascertain. S. J. SHANE

OBSTETRICS AND GYNÆCOLOGY

Function of Aldosterone in the Metabolism of Sodium and Water in Pregnancy.

M. G. RINSLER AND B. RIGBY: *Brit. M. J.*, 2: 966, 1957.

Urinary aldosterone was measured at four-weekly intervals during six normal and three diabetic pregnancies and on one or more occasions between the 28th and 40th weeks of pregnancy in 19 patients with pre-eclamptic toxæmia and in 10 other diabetic patients.

A considerable rise was observed in the amounts of aldosterone recovered from the urine of normal pregnant women as pregnancy progressed. It is suggested that this rise in output is a physiological response by the adrenal cortex to maintain the extracellular fluid volume in the face of loss of sodium and water into the maternal cells and into the products of conception.

A number of diabetic patients were observed to have a considerably greater output of aldosterone from the 28th week of pregnancy onwards than that of a normal group. It is thought that this is due to the greater demand for sodium and water by the tissues of the larger fetus and by the increased volume of the amniotic fluid. A gross reduction in urinary aldosterone was found in pre-eclamptic toxæmia. It is concluded that an agency other than aldosterone is responsible for the further sodium retention and œdema in pre-eclamptic toxæmia.

The effect on aldosterone excretion of a redistribution of sodium and water in the body in certain conditions other than pregnancy is discussed.

Ross MITCHELL

Hypotensive Drugs in Management of Toxæmia of Pregnancy.

R. D. BRYANT: *Postgrad. Med.*, 22: 354, 1957.

The author thinks that vasorelaxing drugs are of great value and may be lifesaving in nearly all cases of moderately severe and severe toxæmia of pregnancy. Because the clinical sign of vasorelaxation is lowered blood pressure, vasorelaxing drugs are sometimes called hypotensive drugs although, ideally, they do not produce hypotension. Conversely, only those drugs which lower blood pressure by vasorelaxation are indicated in toxæmia. These are powerful drugs, but properly used they are safe and effective, have reasonably predictable results, and are theoretically indicated. They also have had extensive clinical trial, and are to date the most satisfactory method of combating the hypertension of toxæmia of pregnancy. The antihypertensive agents used include veratrum derivatives, hydralazine and reserpine. S. J. SHANE

THERAPEUTICS

Treatment of the Acute Asthmatic Attack with an Oral Alcohol-Water Solution of Theophylline (Elixophyllin).

J. SCHLUGER, J. T. MCGINN AND B. BURBANK: *Am. J. M. Sc.*, 234: 28, 1957.

Oral administration of 60 to 75 c.c. of an alcohol-water mixture (20% ethanol) containing in solution 80 mg. of theophylline per 15 c.c. to 50 patients with acute asthma successfully terminated the attacks in 37 (74%). Four of 13 patients who obtained incomplete or no relief were in status asthmaticus and required hospitalization. When the single-dose method was employed, there were very few gastro-intestinal side effects.

The therapeutic advantages of an orally effective xanthine preparation for the treatment of acute asthma are stressed. S. J. SHANE

Effect of Opiates on Activity of Serum Transaminase.

W. T. FOULK AND G. A. FLEISHER: *Proc. Staff Meet. Mayo Clin.*, 32: 405, 1957.

Administration of opiates may be responsible for an increase of serum transaminase activity in some people. Six of 16 patients in this study responded to the hypodermic administration of codeine phosphate (2 grains) with increase of serum transaminase activity that ranged from five to 85 times the control level.

In interpreting increases of serum transaminase activity in the individual patient it is necessary to consider the possible role of opiates administered in the preceding 24 hours.

The mechanism by which serum transaminase activity is increased after administration of codeine has not been adequately explained. Most likely the phenomenon is related to acute spasm of the duodenum and biliary tract. The possibility of associated hepatocellular dysfunction is not excluded.

Very high levels of serum transaminase activity may be encountered in disturbances of the biliary tract under circumstances in which hepatic necrosis is unlikely. S. J. SHANE

Chemotherapy of Tuberculosis: I. Antituberculous Activity of Verazide and Related Hydrazones.

D. S. RUBBO *et al.*: *Am. Rev. Tuberc.*, 76: 331, 1957.

In this paper *in vitro* and *in vivo* studies of isoniazid, Verazide (a chemical variant of isoniazid) and related hydrazones are described. The *in vitro* activity of hydrazone derivatives of isoniazid is equal to that of the parent substance, isoniazid. By using a low critical dosage, 10 mg. per kg. of body weight weekly by intramuscular injection, it is possible to demonstrate differences in chemotherapeutic activity of the various hydrazones. The results of these and other tests showed that Verazide exerted a more marked and more prolonged antituberculous activity than did isoniazid or the other hydrazones. In view of this and of the fact that the hydrazones are generally significantly less toxic than isoniazid, some of these derivatives should be more suitable for the treatment of human tuberculosis than isoniazid itself. Of the hydrazones examined, it appears that Verazide is the drug of choice for clinical application.

The mode of action against the tubercle bacillus exhibited by Verazide and isoniazid is of the same type. Resistant mutants are readily isolated which show complete cross-resistance.

Metal complexes of isoniazid and the copper complex of Verazide were also studied *in vitro* and *in vivo*. All showed marked antituberculous activity and a high local and acute toxicity; hence they cannot be considered as potential chemotherapeutic agents. S. J. SHANE

Evaluation of Digitalis Tolerance with Acetyl Strophanthidin.

L. EHRLICH *et al.*: *Dis. Chest*, 32: 289, 1957.

Experiences in 10 digitalized patients, utilizing acetyl strophanthidin as a digitalis tolerance test, are related. Acetyl strophanthidin exerts its earliest effect within ½ to five minutes, reaches its peak action at 12 minutes, and is dissipated completely in two hours.

In eight of the 10 cases, toxicity could not be elicited with full digitalizing doses of acetyl strophanthidin in previously adequately digitalized patients. This was true whether whole-leaf digitalis or digoxin had previously been employed.

The authors suggest that the acetyl strophanthidin test will indicate whether additional digitalis may be safely administered. It does not, however, indicate the state or adequacy of prior digitalization. One cannot determine by this method, therefore, whether the patient has received any digitalis or is partially or completely digitalized. S. J. SHANE

The Problem of Bioassay and Comparative Potency of Diuretics: II. Carbonic Anhydrase Inhibitors as Oral Diuretics.

R. B. FORD *et al.*: *Circulation*, 16: 394, 1957.

In this study the utilization of controlled metabolic conditions, which furnished the patients with constant dietary and water intake, and measurement of electrolyte and water excretion, as well as weight change, permitted determination of the comparative diuretic potency of orally administered carbonic anhydrase inhibitors.

No significant difference in maximum diuretic effect was found among four carbonic anhydrase inhibitors. The acute response to each of the four carbonic anhydrase inhibitors was approximately equal to 3 tablets (30 mg.) of oral Neohydrin given as a single dose; but continued administration of Neohydrin on consecutive days resulted in an increase in the excretion rate of sodium, while the continued administration of the carbonic anhydrase inhibitors was accompanied by a declining rate of sodium excretion. S. J. SHANE

DERMATOLOGY

Relationship of Atopic Allergy and Dermatitis.

J. S. STRAUSS AND A. M. KLIGMAN: *A.M.A. Arch. Dermat.*, 75: 806, 1957.

The authors review briefly the current concepts concerning the cause of atopic dermatitis. They state that there are three possible etiologic relationships between atopic dermatitis and the atopic state. The first is that atopic dermatitis is a specific cutaneous manifestation of an atopic allergic reaction. Arguments in favour of this are: flareups following injection, inhalation, and ingestion of atopens; avoidance or desensitization may lead to clearing of the lesions. Arguments against this primary etiologic relationship are: flareups produced by exposure to atopens are limited exclusively to previous sites of dermatitis, active or healed, and never occur in new sites; intracutaneous injection of the atopen into the skin does not produce a dermatitis, but a wheal; neither antihistaminics nor epinephrine has any therapeutic effect, as they sometimes do in other

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atopic conditions such as asthma or hay fever. The second possibility is that there is no specific etiological relationship at all. This means that while both atopy and atopic dermatitis may occur in the same patient, this does not prove that one is the cause of the other. The third possibility is that there is a mechanism by which specific atopens can provoke flares of an existing etiologically unrelated dermatitis in susceptible individuals. Thus specific atopens may be an indirect or secondary etiological agent in atopic dermatitis.

In an attempt to demonstrate this third possibility, the authors produced allergic contact dermatitis by applying an extract of poison ivy to the skin of eight atopic patients. They then exposed these patients to intranasal, subcutaneous, and surface application of the specific protein allergen to which they had previously reacted by whealing with scratch tests. They found that, in most cases, there was a flareup of the pre-existing allergic contact dermatitis. The authors suggest that the occasional beneficial effect of hyposensitization in atopic dermatitis and hand eczema is explained as a result of the removal of such secondary aggravating factors. ROBERT JACKSON

Treatment of Keloids.

J. C. BELISARIO: *Acta dermato-venereol.*, 37: 165, 1957.

There is a brief review of the recent literature on keloids including the use of injections of hyaluronidase and/or hydrocortisone with or without radiotherapy. The author treated 114 keloids by various methods including radiotherapy, scalpel surgery or electrosurgery, intralesional injections of hydrocortisone and/or hyaluronidase, and combinations of the above. He found the six-month cure rate with radiotherapy alone to be 10%; the six-month cure rate with combined injections, scalpel or electrosurgery and radiotherapy was 80%. Other cure rates were intermediate between these two. Combined therapy (i.e. by surgery, hydrocortisone and hyaluronidase) is recommended. Recurrences commenced within three months of completion of treatment and none were noted after six months. No improvement was noted from use of hydrocortisone ointment alone or combined with hyaluronidase. ROBERT JACKSON

Electrodesiccation of Pigmented Nævi.

R. G. WALTON, R. D. SAGE AND E. M. FARBER: *A.M.A. Arch. Dermat.*, 76: 193, 1957.

One hundred and sixty-eight pigmented skin lesions were treated by electrodesiccation after the upper portion of the lesion had been shaved off for biopsy; 112 of the sites were biopsied again at intervals of 3 to 12 months. The histopathology of these second biopsies showed no evidence of malignant degeneration. In most cases the nævi were found to have been completely destroyed, and in some the nævus cells were buried in scar tissue. Recurrence of pigment in treated sites was common and did not indicate that malignant change was occurring. The authors conclude that "shave biopsy" followed by electrodesiccation is a safe procedure and gives a much superior cosmetic result, especially with multiple lesions. The importance of a biopsy at the initial treatment is stressed. The authors clinically misdiagnosed 7.1% of the pigmented lesions.

Junction nævi or nævi showing growth, darkening, recent appearance, or ulceration were excluded. In the authors' opinion these lesions should be completely excised. ROBERT JACKSON

Morphea-like Epithelioma.

J. B. HOWELL AND M. R. CARO: *A.M.A. Arch. Dermat.*, 75: 517, 1957.

The authors claim that this is a rare condition. Many previously reported cases were examples of epitheliomas with a large component of scar due to treatment, infection, injury or other cicatrizing disease process. Clinically the lesion presents as a smooth, wax-like, yellowish-white, leathery, indurated area usually on the head or neck. There is no pearly border. Ulceration and crusting are infrequent. There are occasional telangiectatic vessels on the surface. The lesion starts in childhood or early adult life and grows extremely slowly. Solitary lesions are the rule. It does not occur in conjunction with farmers' or sailors' skin. Histopathology shows many narrow strands of basal cell cancer lying in a densely packed connective tissue stroma. The differential diagnosis includes morphœa, localized senile elastosis, chronic discoid lupus erythematosus, and superficial cicatrizing epithelioma. Treatment is by surgical excision, low intensity radium needles or Mohs's chemosurgical technique. ROBERT JACKSON

Vesicular Dermatitis of the Palms Caused by Colchicine.

L. HOLLANDER: *A.M.A. Arch. Dermat.*, 73: 872, 1957.

In a case of vesicular dermatitis on the hands and fingers of a 51-year-old man, the eruption failed to respond to all conventional methods of therapy. Then all medication including colchicine, which he was taking for gout, was stopped. Within two weeks his hands were clear. A subsequent attack of gout was treated by 12 doses (0.6 mg. per dose) of colchicine during a three-day period. At the end of this time he had a severe vesicular dermatitis in the same areas. The colchicine was stopped and within eight days his dermatitis was almost gone. ROBERT JACKSON

INDUSTRIAL MEDICINE

Screening for Eye Disease.

F. M. FOOTE: *A.M.A. Arch. Indust. Health*, 16: 254, 1957.

Inclusion in industrial periodic examinations of tests for early detection of eye disease can make an unparalleled contribution to the nationwide effort to prevent unnecessary loss of sight. Not only can one note local conditions of the eyes themselves, but opportunity is provided for early detection of general disease, such as diabetes, hypertension, arteriosclerosis, and nephritis.

Four methods are described for finding eye disease early: taking visual acuity at distance and near; doing ophthalmoscopic examination of the fundus periodically; taking intraocular tension with a standardized tonometer; and doing a screening test for field of vision on persons over 35 or 40 years of age.

Lowered visual acuity is a sign of eye disease or perhaps of general systemic disease affecting the eyes, as well as being an indication of a

refractive condition. There have been reports that from 4% to 6% of employed persons with lowered visual acuity alone have some pathologic lesion in the eyes which requires the care of an oculist.

Use of the ophthalmoscope can not only detect such signs of trouble as opacities in the lens or separation of the retina, but may often be of great value in revealing the status of any vascular disease that may be present.

Tonometry is used to detect chronic simple glaucoma. This form of glaucoma is far more prevalent than the acute type. It is symptomless and insidious. Early detection is the only way to reduce the economic burden of blindness from this cause. Several industrial and community-wide screening surveys reported in recent medical literature have indicated an incidence of approximately 2%.

In connection with the examination of visual fields, reference is made to a new type of screening device which permits a rough screening test in less than five minutes. MARGARET H. WILTON

Hazards from Agricultural Chemicals.

Editorial: *Brit. M. J.*, 1: 875, 1957.

This article presents a brief review of hazards from agricultural chemicals as reported in recent literature. In agricultural work the chemicals used range in their toxicity to man from the very dangerous such as parathion and dinitro-orthocresol (D.N.O.C.) to the virtually harmless. The choice of any particular one, however, is determined by factors other than danger to the user.

In Great Britain co-operative effort by many people including manufacturers, distributors, and officials of the Ministry of Agriculture has produced a good record in the safe use of the more dangerous pesticides. Consideration, however, must be given to experience elsewhere. For example, 28 cases of poisoning by organo-phosphorus insecticides were recorded among agricultural workers in Germany during the period 1950-1955. These included one fatal, three severe, seven moderate and 17 mild cases. The most frequent symptoms were headache, dizziness, weakness, nausea, and vomiting.

In all suspected cases of poisoning by organophosphorus insecticides atropine must be given in large doses. Should a mild case respond well to this therapy, the patient must be kept under observation for 12-24 hours because a single dose of atropine may be of only temporary benefit. For D.N.O.C. poisoning there is no specific treatment. The chlorinated hydrocarbon group of insecticides are being used in agriculture without any apparent difficulties.

For some years antibiotics, including penicillin and streptomycin, have been used as supplements to pig and poultry feeds. More recently in the United States sprays containing streptomycin have been applied to certain crops to control plant diseases due to micro-organisms. Although so far there have been no reports of ill effects among agricultural workers, the risk of handling antibiotics in this way must be recognized.

It is suggested that the doctor with agricultural workers among his patients should ask about possible exposure to toxic chemicals when cases of vague illness are reported to him.

MARGARET H. WILTON

Gamma Radiography in Industry.

J. P. W. HUGHES AND O. SHAW: *Brit. J. Indust. Med.*, 14: 183, 1957.

The use of x-rays has for a long time been a familiar technique in the medical world. Their application to metals and other structures in industry is also of fairly long standing. Gamma radiography, however, was not widely practised in industry until artificial isotopes became commercially available soon after World War II. This paper describes its use in testing boilers indestructively in the North West Division of the Central Electricity Authority. By this method metal failure can be anticipated in installed apparatus and danger of boiler explosions is thereby reduced. The author describes also the protection of persons exposed to radiation.

The isotopes used were cobalt and iridium; iridium was the more satisfactory on account of its softer radiation. Details are given regarding the apparatus and the methods of using the isotope sources within boiler drums. Examples of exposure calculation are included.

Protection of the people comprising the testing team is important. They are required to carry on their persons apparatus to estimate the dose received, particularly in the parts of the body likely to be most irradiated. There are acceptable dosage levels per unit time and these must on no account be exceeded. Two methods of monitoring are followed: (a) the wearing of a "fountain-pen" type of dosimeter, and (b) the wearing of film badges on lapel and wrist. A weekly limit of 0.3 r and a moving average of 0.1 r per week over 13 weeks were laid down as maximum permissible doses for this work. By using the dosimeters individuals can assess their dosage; if they reach 0.3 r they are automatically suspended from further exposure. Routine blood counting as a means of assessing exposure is discussed from a critical point of view. Medical opinion today appears to be inclining more and more towards discarding it.

In the period under review no cases of illness due to exposure or serious overexposure occurred. The men employed on the team were between 18 and 45 years of age. Each was given a thorough general medical examination to determine fitness for this work. A detailed record of sickness and accidents was kept to exclude the accident-prone individuals and to clarify doubtful sickness records. Individual charts of dosimeter and film badge readings were maintained in the medical department and readings of both dosimeter and film badges were known to both engineers and the medical adviser. The team leader or his deputy was able to exclude men from radiation without waiting for medical advice. MARGARET H. WILTON

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OBITUARIES

DR. FREDERICK WILBUR JACKSON

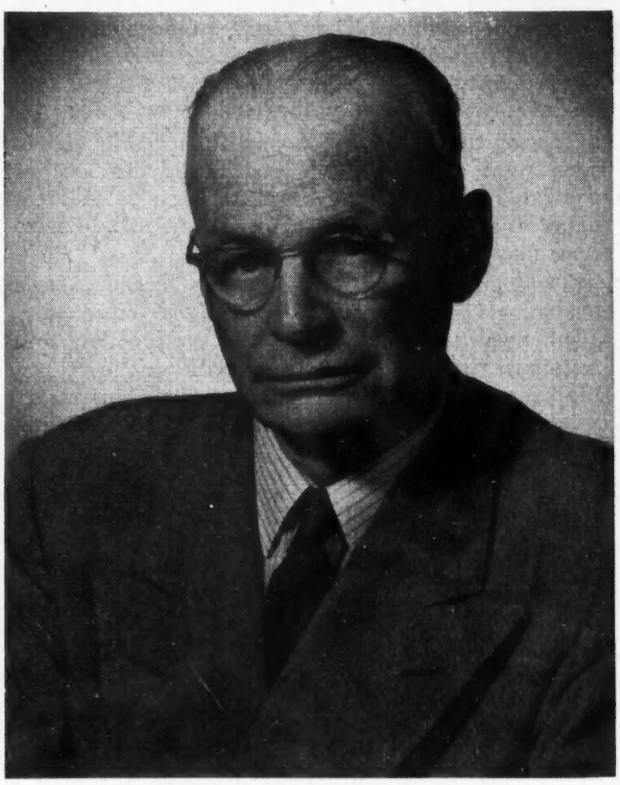
AN APPRECIATION

The passing of Dr. Frederick Wilbur Jackson at his home in Winnipeg on January 10, at the age of 69, will be mourned by his many friends and colleagues throughout Canada and the United States. Fred Jackson, as he was popularly known, displayed the best characteristics of the country doctor and the skilled public health administrator. His outstanding contribution to medical care and public health in Canada will long be remembered. Many honours and awards were conferred upon him during his forty years in the health field.

Born in Stonewall, Manitoba, Fred Jackson graduated in medicine from the University of Manitoba in 1912 and obtained the Diploma in Public Health from the University of Toronto in 1929. From 1912 to 1927 he practised medicine in rural Manitoba except for the four-year period 1914-18 when he was overseas with the Canadian Expeditionary Forces, serving with the No. 5 Canadian General Hospital in Salonika, Greece, and England. He was invalided home in March 1918, because of malaria.

In 1928 Dr. Jackson entered the Department of Health and Public Welfare of the Province of Manitoba, where he served from 1931 to 1948 as Deputy Minister of Health and Public Welfare. During that time, from 1928 to 1937, he was part-time Field Secretary of the Manitoba Division of the C.M.A., taking an active part in the conjoint Annual Meeting of the B.M.A. and C.M.A. held in Winnipeg in 1930. His activities in the public health field were many, and his vision and program were usually in the forefront of public health thinking. From 1939 to 1948, Dr. Jackson was Professor of Preventive Medicine at the University of Manitoba, and for several years gave special lectures at the School of Hygiene, University of Toronto.

In 1943 he was appointed by the federal government as chairman of a royal commission to investigate the health and welfare of the Japanese people in the interior of British Columbia, and from 1942 to 1945 he was a member of the Manitoba advisory committee of the Canadian Medical Procurement and Assignment Board. In 1948 he represented Canada at the fifth meeting of the interim commission of the World Health Organization in Geneva, and while overseas spent some time studying the United Kingdom's health insurance and social security plans. He was appointed director of health insurance studies in the Department of National Health and Welfare in August 1948, and a few years later became Director of Health Services in that department. His administration of the National Health Grants program in extending hospital, diagnostic and public health services throughout Canada has been recognized as a major contribution to Canadian health services. His subtle humour, wise leadership, and breadth of vision were always a stimulus to those he worked with. Dr. Jackson's numerous contributions to the literature and many speaking engagements made him very well known to medical and public health audiences in Canada and the United States.



Dr. Frederick Wilbur Jackson

He was a member of the Manitoba and the Canadian Medical Associations; the Winnipeg Medical Association; the American Public Health Association; the Canadian Public Health Association, of which he was president in 1935; the State and Provincial Health Authorities of North America, serving as vice-president in 1937 and president in 1942; and a member of the Board of Examiners of the Medical Council of Canada. He was a member of the Post-Graduate Committee of the University of Manitoba's Medical Faculty and of the Central Council of Social Agencies for Greater Winnipeg, of which he was vice-president from 1935 to 1948. In 1941 he was appointed an Honorary Life Member in the Association of Military Surgeons of the United States. In 1950 he was made an Honorary Life Member of the Conference of State and Provincial Health Authorities of North America. More recently, in 1956 Fred Jackson was made an Honorary Life Member in the Canadian Public Health Association and in 1957 a Senior Member of the University of Toronto School of Hygiene Alumni Association. He was a certificated specialist in public health by the Royal College of Physicians and Surgeons of Canada.

The awards received by Fred Jackson include the King George V Silver Jubilee Medal and the King George VI Coronation Medal for Meritorious Civil Service. In 1950 he was awarded the Medal of the Professional Institute of the Civil Service of Canada for outstanding achievement in the field of public health and welfare. In 1956 he was awarded the Sedgwick Memorial Medal by the American Public Health Association for distinguished service in public health.

Fred Jackson will be counted among the great men of public health in Canada and his presence will be greatly missed.

DR. DANIEL LEO KENNEDY, 65, died at his home in Hamilton, Ont., on December 22, 1957. Dr. Kennedy was born in Portsmouth, Ont., and received his medical education at Queen's University, where he graduated M.B. in 1914. He served with the Royal Canadian Army Medical Corps from 1914 to 1919 when he returned to Queen's University and graduated M.D., C.M. Dr. Kennedy started practice in Saskatchewan and from 1929 to 1931 he attended the Brooklyn Eye and Ear Hospital. From 1931 until his retirement three years ago he practised in Hamilton, Ont.

Dr. Kennedy is survived by his widow, two sons and three daughters.

DR. HOWARD WILLIAM DAVID McCART, assistant professor of the department of otolaryngology, University of Toronto, died on January 8. He graduated in medicine from the University of Toronto in 1921 and continued his postgraduate studies at Toronto General Hospital and in Edinburgh and Vienna. In 1939 he joined the Royal Canadian Medical Corps and served overseas with the 15th Canadian General Hospital as a specialist and consultant in otolaryngology. He retired from the army with the rank of lieutenant-colonel. Dr. McCart was consultant at Christie Street and Sunnybrook Hospitals and at the Cancer Institute.

He is survived by his widow, two sons and two daughters.

DR. ERNEST SAMUEL MOORHEAD, 81, died suddenly on December 22. Born in Dalkey County, Ireland, he received his degree in medicine from Trinity College, Dublin, in 1901 and came to Canada in that year to practise in Winnipeg. In the first World War he served overseas as medical officer of the 189th Brigade Field Artillery.

For thirty-five years he was C.P.R. surgeon. In 1924 he was president of the Winnipeg Medical Society when the first Gordon Bell Memorial lecture was delivered by Dr. J. B. Collip. He served on the honorary attending staff of the Children's and Winnipeg General Hospitals and was associate professor of medicine in Manitoba Medical College.

Always interested in social medicine, he was chairman of the Welfare Supervision Board and first secretary of the Manitoba Hospital Service Association. During the depression years he was chairman of the board which set up the Winnipeg Unemployed Medical Relief Plan and subsequently he supervised the medical aspects of the scheme. Later he helped to set up the Winnipeg Firefighters Medical Scheme which was a forerunner of the Manitoba Medical Service. The Manitoba Medical Association set up a Sociology Committee with Dr. Moorhead as Chairman. The recommendations of this committee set up the framework for Manitoba Medical Service. For four years Dr. Moorhead was the medical director.

His widow, a son, two daughters and five grandchildren survive him.

DR. CLIVE NEILSON, 57, died December 28. Born in Kenora, Ontario, he went to Winnipeg as a child, and graduated in medicine from the University of Manitoba in 1928. He practised in Winnipeg as a general practitioner and anæsthetist.

He was an outstanding athlete and from 1916 to 1928 had few equals in track and field. In 1924 he was the Canadian decathlon champion and he also played football and baseball. For many years he was examining physician for the Manitoba Boxing and Wrestling Commission.

He was active in the Y.M.C.A. and Masonic organizations; a past president of the Native Sons of Canada and a member of the Manitoba Pipers Association.

His widow and three daughters survive him.

DR. W. H. PERRY, 45, died on December 25, 1957, at Vancouver General Hospital. Dr. Perry was born in Halifax, N.S., and received his medical education at the University of Toronto where he graduated in 1939. He served an internship at Vancouver General Hospital and became assistant medical director of the outpatient department. From 1941-1946 he served as a captain in the R.C.A.M.C. in Canada and in Europe. In 1946 he became resident in medicine at Shaughnessy Hospital, Vancouver, and was an intern in pathology at McGill University from 1947 to 1948, when he took up postgraduate studies at the Royal Infirmary, Glasgow, Scotland. Dr. Perry returned to Vancouver in 1949 and was appointed hæmatologist in the department of pathology at Vancouver General Hospital and assistant professor in the department of medicine at the University of British Columbia. Dr. Perry was actively interested in research and was co-holder of a grant from the National Cancer Society. At the time of his death he was setting up a research project on vitamin B_{12}.

He is survived by his widow and two sons.

FORTHCOMING MEETINGS

CANADA

COLLEGE OF GENERAL PRACTICE OF CANADA, Second Scientific Assembly, Winnipeg, Man. (Dr. W. V. Johnston, Executive Director, College of General Practice of Canada, 176 St. George St., Toronto 5, Ont.) April 14-16, 1958.

CANADIAN OTOLARYNGOLOGICAL SOCIETY (SOCIÉTÉ CANADIENNE D'OTOLARYNGOLOGIE), Annual Meeting, Halifax, N.S. (Dr. Donald M. MacRae, 324 Spring Garden Road, Halifax, N.S.) June 9-11, 1958.

CANADIAN TUBERCULOSIS ASSOCIATION, 58th Annual Meeting, Quebec City, P.Q. (Dr. G. J. Wherrett, Executive Secretary, Canadian Tuberculosis Association, 265 Elgin St., Ottawa 4, Ont.) June 9-12, 1958.

CANADIAN MEDICAL ASSOCIATION, 91st Annual Meeting, Halifax, Nova Scotia. (Dr. A. D. Kelly, General Secretary, The Canadian Medical Association, 150 St. George Street, Toronto 5, Ont.) June 15-19, 1958.

UNITED STATES

AMERICAN COLLEGE OF SURGEONS, Sectional Meeting, New York, N.Y. (Dr. H. P. Saunders, Associate Director, American College of Surgeons.) March 3-6, 1958.

AMERICAN ORTHOPSYCHIATRIC ASSOCIATION, 36th Annual Meeting, New York, N.Y. (Dr. Marion F. Langer, Executive Secretary, American Orthopsychiatric Association, 1790 Broadway, New York 19, N.Y.) March 6-8, 1958.

AMERICAN ACADEMY OF GENERAL PRACTICE, Annual Meeting, Dallas, Texas. (Mr. Mac F. Cahal, Executive Secretary, Volker Boulevard at Brookside, Kansas City 12, Mo.) March 24-27, 1958.

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PROVINCIAL NEWS

ONTARIO

The Canadian Red Cross Society has taken the responsibility for supplying blood for transfusions to the 19 public hospitals in Metropolitan Toronto. To meet the demand, donors must provide 1500 to 2000 pints each week. Blood more than three weeks old is not used for transfusion but the plasma is fractionated into serum albumin, gamma globulin and fibrinogen for appropriate use.

Dr. Grace Baker, associate psychiatrist, Columbia University, addressed an open meeting of the staff of Women's College Hospital, Toronto, on "The Integration of Psychiatry in Medical Practice".

Dr. Ford Connell, professor of medicine, Queen's University, and his associate, Dr. George A. Mayer have received a grant of $6700 from the Schering Corporation towards their work on anticoagulant agents in the treatment of coronary thrombosis. At present they are investigating the effects of anticoagulants other than their anti-clotting action.

Mr. C. L. King, Toronto, has been elected president of the Ontario division, Canadian Cancer Society. The division contributed $249,123 to the National Cancer Institute in support of its fundamental research program. Clinical investigation through the national office also was supported by $19,580, and $64,584 was contributed to the Ontario Cancer Treatment and Research Foundation for extension of clinical treatment and research facilities.

Dr. E. A. McCulloch addressed the Cancer Society's annual meeting on leukæmia. He said that exciting new evidence has been found in support of the old idea that leukæmia might be a kind of infection due to a particular and different kind of virus. The theory of infection has been unpopular for two reasons: It was hard to imagine an infection capable of altering the nucleus and heredity of the cell, and nobody had been able to find any infectious agent or virus in cells or serum of leukæmia patients.

New information has revealed that viruses are able to enter cells of bacteria and hide there by attaching themselves to the genetic mechanism, the nucleus. They become indistinguishable from the rest of the genetic mechanism and are passed on to progeny of the original cell. When subject to certain insults, x-rays and chemicals capable of inciting cancerous growths, they emerge from hiding and destroy the cells in which they were hiding and infect other cells. This answers the first objection to the infection theory of leukæmia.

The second objection was answered by the work of Dr. Ludwig Gross, New York, who found that when he injected the extract of leukæmia tissue into mice within a few hours of birth, they developed leukæmia when they became adults. This was a new kind of infection, an infection not capable of transmission to an adult but effective in a newborn mouse, and able to hide in the mouse for most of its adult life and later cause disease.

Life memberships in the Essex County Medical Society have been given to Dr. E. Kirk Lyon and to Dr. Murray S. Douglas in recognition of their service during their terms of office as presidents of the Ontario Medical Association.

Dr. Ben Lubarsky has been elected president of the Society. Dr. G. A. McTague has been named as the representative on the Senate of Assumption University.

LILLIAN A. CHASE

NEW BRUNSWICK

Dr. Mary Southern Holt has been appointed Director of the Maternal and Child Health section of the New Brunswick Department of Health to succeed Dr. J. R. Mayers, who resigned recently. Dr. Holt has held many public health appointments in Britain and South Africa. She is a graduate of the University of Capetown.

The first cobalt bomb in the Maritime Provinces is being installed in the new radiotherapy department of the Saint John General Hospital as a result of cooperation between the Provincial and Federal Governments, the Canadian Cancer Society and hospital authorities. The radiotherapy department in the hospital is supervised by Dr. J. A. Caskey and his assistant director, Dr. G. D. Smith.

The annual announcement of staff positions at the Saint John General Hospital shows that Dr. R. M. Pendrigh has been promoted from Chief of Service in Surgery to the consulting staff. Dr. J. P. McInerney becomes Chief of Staff in Surgery. Dr. H. A. Bird is Director of Pathology and Dr. J. Riives is appointed to the Department of Neurology and Psychiatry.

Dr. George H. Blennerhasset has been appointed Superintendent of the Moncton Tuberculosis Hospital to succeed Dr. P. M. Knox, deceased. The new appointee has had large experience in chest diseases in Britain, U.S.A. and Ontario.

The Hon. J. F. McInerney, M.D., Minister of Health and Social Services, has announced the establishment of an interim study committee which is to undertake a study of facts and figures on a hospital insurance plan for the Province of New Brunswick. The committee is to submit a report of the study upon its completion to the Minister of Health and Social Services.

The committee is composed of seven members under the chairmanship of Mr. B. Guss, Q.C., Saint John. The members are: Dr. C. R. Trask, Director, Saint John General Hospital; Rev. Mother St. George, Provincial Bursar, Religious Hospitalers of St. Joseph; Mr. D. O. Downing, Associate Director, Maritime Hospital Services Association; Mr. William McNichol, Assistant Comptroller General, Department of the Provincial Secretary-Treasurer; Dr. C. W. Kelly, Director of Health Planning Services, Department of Health and Social Services; and Mr. R. Bennett, Moncton.

On January 16, Dr. H. B. Atlee of the Medical School of Dalhousie University paid a visit to the Saint John Medical Society, during which he acted as guest consultant at a clinical conference in the obstetrical

(Continued on page 302)

Another clinical evaluation of Mio-Pressin* in hypertension

Salient observations:

- "Since hypertension may be caused by a variety of factors influencing several body mechanisms, it is generally believed that a combination of drugs, each having a different site of action, is more likely to be effective than any one drug alone."

- "Eighty-nine per cent of the patients [in this evaluation] had become normotensive by the conclusion of the study."

Smith, C.W., and Thomas, C.G.:
Am. Pract. & Digest Treat.
8:920 (June) 1957.

'Mio-Pressin'—a balanced combination of rauwolfia, protoveratrine and Dibenzyline*—for moderately severe to severe hypertension, in two dosage strengths: No. 2 (standard strength) and No. 1 (half strength).

Smith Kline & French · Montreal 9

8140

*Reg. Can. T. M. Off.

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department of the Saint John General Hospital. In the evening of the same day, Dr. Atlee spoke on "Chronic Iliac Pain in Women" in the auditorium of the laboratory building. The large audience enjoyed the interesting address by this friendly Maritime teacher who is always welcomed where physicians foregather.

A. S. KIRKLAND

NOVA SCOTIA

The Victoria General Hospital had the pleasure of a visit early in December from Dr. R. S. Allison, lately of the Royal Infirmary, Belfast, Northern Ireland. During his visit here Dr. Allison spoke to the staff of the Victoria General Hospital on neurological problems. For some time now Dr. Allison has been interested in research in disseminated sclerosis and allied conditions. This research work is being conducted at Charleston, S.C., and also in the Halifax area.

Dr. Hugh N. A. MacDonald has opened an office for the practice of neurology at the Medical Arts Building, Halifax. Dr. MacDonald graduated from the Dalhousie Medical College in 1953. He spent three years at the Mayo Clinic in his specialty. The year 1957 was spent at the Montreal Neurological Institute as a Teaching Fellow. He was successful in obtaining his certification.

Dr. James Alan Myrden, a member of the surgical staff of the Victoria Hospital, Halifax, has recently been awarded his certificate in surgery by the Royal College of Physicians and Surgeons of Canada.

WALTER K. HOUSE

PRINCE EDWARD ISLAND

At a meeting of the Medical Society of Prince Edward Island on Wednesday, January 8, the guest speakers were Mr. Ian Campbell of Ottawa, National Co-ordinator of Civilian Rehabilitation, and Dr. B. Primeau of the Department of National Health and Welfare. Both spoke on medical rehabilitation, after a dinner and business session of the Society at the Charlottetown Hotel. Mr. Campbell and Dr. Primeau visited the province for two days at the invitation of the Medical Society to assist in the study of rehabilitation needs and to plan a program in co-operation with the Medical Society, the provincial department of health and other interested agencies.

Dr. Malcolm J. Putnam, formerly of Brockville, Ontario, has joined the surgical staff of the Polyclinic in Charlottetown. Dr. Putnam was born in Vancouver and educated at Mount Allison and McGill universities. He obtained his F.R.C.S.[C.] in 1949 after the diploma course in surgery at McGill.

J. A. MCMILLAN

QUEBEC

Dr. Fernand Montreuil gave a paper on "Carotid Body Tumours" at a meeting of the eastern section of the American Laryngological, Rhinological and Otological Society held in Philadelphia in January 1958.

BOOK REVIEWS

PNEUMOENCEPHALOGRAPHY. E. Graeme Robertson, Melbourne, Australia. 482 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $16.00.

This is a new, profusely illustrated monograph dealing with both normal and abnormal pneumoencephalograms. The first hundred pages describe the distribution of gas, the mechanism of ventricular filling, experiments with hollow ventricular models, application of principles to practice, pneumoencephalographic technique and the appearance of normal intracranial structures in standard projections. They are outstanding because of the clarity of descriptions and the excellence of the illustrations. Many of the plates appear to be the original plates from the author's previous monographs "Encephalography" and "Further Studies in Encephalography". Dr. Robertson's hypothesis explaining ventricular filling may not be completely acceptable to everybody but this detracts little from the introductory chapters. He suggests that gas in the cisterns and the sulci is responsible for the headache in encephalography. However, all experienced operators have had patients complain of severe headache during attempted pneumoencephalography in which radiographs failed to show any gas within the cranium.

A very fine chapter on "Failure of Ventricular Filling: Implications and Rectification" follows. The next 200 pages describe the ventricles and subarachnoid spaces and their deformities by tumours and adhesions. This has been handled on an almost purely descriptive basis. The descriptions of the ventricles and subarachnoid spaces are excellent. The case histories, photographs of pathological specimens, radiographs, and diagrams are good. Unfortunately the author does not give any critical discussion of criteria for diagnosis and localization of tumours in various locations or of the value of the various measurements he has listed in several chapters. It is in these two areas that students of radiology, neurology, and neurosurgery need the most help. The last 150 pages deal with diverse subjects, of which hydrocephalus and developmental abnormalities are done very well.

The author concludes by saying that he prefers ventriculography or angiography in brain tumour. He minimizes the value of pneumoencephalography in epilepsy, but states that this is his personal opinion and that in other centres different ideas are held.

PLASTIC ARTERIAL GRAFTS. W. Sterling Edwards, Medical College of Alabama, Birmingham, Ala. 126 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $5.00.

The rapid expansion of vascular surgery in the last few years has made this volume summarizing Dr. Edwards's experimental and clinical experiences with vascular grafts timely and invaluable. An excellent résumé of the history of vascular grafting is given; the various materials tried, the problems arising with various materials, and the various methods are discussed. The preliminary search for ideal materials, and the fashioning of the braided, crimped nylon graft, are described, and there is a brief discussion of the various vascular injuries and their care, stressing the need for early diagnosis and definitive treatment. The

management of various aneurysms and the use of grafts in segmental obstructive arteriosclerosis are dealt with fully, line drawings and photographs providing excellent illustrations of methods. The chapter on the surgery of the thoracic aorta outlines excellently the current methods and problems. In the final chapter the author freely admits the need for much more research in this field and outlines the problems unanswered as yet.

Though the crimped, braided nylon graft may not be the final answer for those seeking an easily sterilized, readily available, easily handled and apparently long-lasting vascular graft, the work outlined here presents it as a very useful interim substitute for homografts, which carry their own attendant difficulties of procurement, care and handling. In Edwards's hands the nylon graft has not been liable to early thrombosis, it does not lose strength *in situ*, it will not collapse or kink, and apparently, unlike homografts, it may not become atheromatous.

CHEMICAL ANTHROPOLOGY: A New Approach to Growth in Children. Icie G. Macy and Harriet J. Kelley. 149 pp. The University of Chicago Press; University of Toronto Press, 1957. $3.75.

This book on chemical anthropology or chemical growth and its relationship to physical growth and physiologic function in children is an extremely detailed observational study based on 11 children in a home for children who were studied for 95 days, and in a second period four years later for 225 days; after another four years seven of the same children were studied for a further 55 days. These children were studied and observed constantly and detailed evaluations made of their physical growth, mental growth and particularly their chemical growth. Chemical growth was studied by detailed recordings of all food intake, chemical examinations of all excreta, metabolic balances, basal oxygen consumption, basal heat production, estimation *in vivo* of body composition, detailed studies on the retention and absorption of nitrogen, calcium and phosphorus at each of the age levels, daily energy exchange, daily protein exchange, etc. This is an extremely detailed study, the first of its kind that has been done in children, and will be of value to nutritionists and those intimately concerned with growth in children. It is, however, too complicated and detailed to be of interest to the practising physician.

THE CINCINNATI DOCTORS' FORUM. Reginald C. McGrane, University of Cincinnati. 389 pp. The Academy of Medicine of Cincinnati, Cincinnati, Ohio, 1957.

This volume is ostensibly the history of the Academy of Medicine of Cincinnati, but is in fact a history of the practice of medicine of the United States from the point of view of that Academy. A casual glance might suggest that this is local history of no interest outside the local area, but on further examination it becomes evident that the medical world of Cincinnati during the past century has been characteristic of medical practice in most parts of North America. It recounts the effect of ignorance, indifference, quackery and personal feuding upon the welfare of the community and the reputation of the medical profession. It traces the gradual growth of the medical community from a small group in the 1850's to a large modern medical society and shows how the aspirations and efforts of a few dominant individuals have led to the development of modern North American medical practice. This history is not limited to the area of greater Cincinnati, but inevitably spills over into national and international affairs.

This volume should prove of interest to all historians, both medical and non-medical, who are interested in the social development of the United States during the past century.

LEHRBUCH DER HAUT – UND GESCHLECHTS-KRANKHEITEN (Textbook of Dermatology and Venereal Diseases). Walther Schönfeld, Heidelberg, W. Germany. 513 pp. Illust. 7th ed. Georg Thieme Company, Stuttgart; Intercontinental Medical Book Corporation, New York, 1956. $10.50.

This is the seventh edition of a standard textbook of dermatology in the German language. The book has always treated dermatology and venereology from the practical rather than the academic standpoint; in consequence sections on diagnosis and therapy are detailed, while pathology and histology are only very briefly mentioned. In this new edition, therapy has been brought up to date, with particular reference to isotope and steroid therapy. There is a new chapter on the investigation of male fertility and new material on melanoma and carcinoma. The work has always been profusely illustrated, and the new edition carries even more black-and-white photographs than before.

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HYPOPHYSECTOMY. Edited by O. H. Pearson, Associate Professor of Medicine, Cornell University Medical College, New York. 154 pp. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $5.50.

In March 1956 a conference was held at the Sloan-Kettering Institute in New York to evaluate the potential of hypophysectomy for advanced cancer. This book, containing the papers and discussion of the 24 participants, is essentially a progress report. It represents perhaps one of the more remarkable clinical research programs into the hormonal control of cancer, a study from a number of medical centres of a total of some 340 patients subjected to destruction of the pituitary gland by surgery or radiation.

There are four main chapters on surgical hypophysectomy in patients with cancer, surgical hypophysectomy in diabetic patients, physiological effects of hypophysectomy, and radiation hyphophysectomy. Each is followed by a discussion, and these sections point up the editorial difficulty of verbatim reporting of remarks which may vary from the interesting to the desultory. The most impressive results are presented in the two larger series, one from Stockholm and the other from New York, of patients who had surgical removal of the gland by frontal craniotomy. About half of these had dramatic remissions which continued in some cases for over two years. The main problem is the technical one of destroying the gland completely or "functionally completely" without damage to the closely adjacent optic nerves or overlying hypothalamus. Insertion of multiple radioactive pellets into the gland, either intracranially or transnasally, offers a seemingly simple but so far less reliable and more hazardous technique. One group reports that it is established that a dose of radon sufficient to necrose the pituitary completely will damage more radiosensitive structures outside the pituitary fossa. Radon seeds have therefore been abandoned because of the complication of blindness or hypothalamic symptoms.

Radioactive yttrium, giving off short-range beta radiation, has shown promise, but complete destruction of the gland seems difficult to attain consistently. The percentage of remissions reported in any series using radiation is so far much less than in the two most successful groups subjected to surgical removal of the gland. One report makes it clear that external radiation was of little use for selective destruction of the pituitary.

Most of the series reported in this monograph are restricted to the treatment of advanced cases of female breast cancer but sporadic remissions in cancer of the male breast and prostatic cancer are noted. Some benefit from surgical hypophysectomy was also reported in young patients with advanced diabetes.

Little information can yet be offered as to the basis for the dramatic remission or for the inevitable recurrence in these patients who do show remission. It is of interest that hypophysectomy may give a remission when adrenalectomy or oophorectomy, or both, has previously given remissions. Growth hormone has been implicated on several counts as a factor in breast cancer growth. The availability over the past few years of limited quantities of tumour growth hormone preparations holds promise for another informative chapter in the study of hormonal control of cancer.

The individual reports vary widely in the amount of information presented but any physician or medical investigator concerned with the problem of cancer will find this book of interest. There are 24 tables and a bibliography of 30 references, but no index. The book is not illustrated.

THE EARLY DIAGNOSIS AND TREATMENT OF ACOUSTIC NERVE TUMORS. J. Lawrence Pool, Professor of Neurological Surgery, Columbia University, New York, and Arthur A. Pava, Assistant Neurological Surgeon, Wesson Memorial Hospital, Springfield, Mass. 161 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $6.00.

Drs. Pool and Pava anticipate the inevitable question, "Why another book on acoustic neuromas after Cushing's monumental work?" by some remarks in the opening sentences of the introduction which amounts almost to an apologia. But that mood quickly changes and they settle down to a very good presentation of the experience of the Neurological Institute, New York, in the treatment of this type of tumour. There are references to all the important contributions in the literature that have preceded this one. In an art as plastic as medicine no one ever has the last word and, while the studies of earlier authors are familiar to present-day practitioners, the latter badly want to know how their contemporaries are tackling the same problems and with what success. This is a short monograph, modest and unpretentious, but full of important information. It is not a landmark in the treatment of acoustic neuromas but a good, business-like, factual survey of how in one famous institution they manage these cases.

In the introduction the authors say that early diagnosis is important and they suggest that greater familiarity with the syndrome of the acoustic neuroma will result in earlier diagnosis, and early diagnosis means early treatment with consequently better results. However, there is nothing in their tables and figures to support this view. In the analysis of the operative deaths there are four records of death from brain stem œdema but, as the authors admit, no adequate estimate could be made from the operation record of the size of the tumour. Nor is there any information on the duration of symptoms before diagnosis was made or treatment undertaken. Every neurosurgeon has had experience of the so-called early acoustic neuroma with only the slightest of signs that turns out to be a large tumour. The reviewer wonders whether in fact much is to be gained from striving for earlier diagnosis (a dangerous, not to say heretical attitude, this). Improvement will come about, as it has in the past, rather from innovations in surgical technique and postoperative management. It is interesting to see that the results following total tumour removal were superior both in terms of mortality and morbidity (and, of course, of recurrence) to the results following the more conservative procedure of intracapsular enucleation advocated so vehemently by Cushing.

DOCTOR IN LOVE. Richard Gordon. 188 pp. Michael Joseph, Don Mills, Ont., 1957. $3.00.

The latest addition to the "Doctor" series takes the hero a further step on his hilarious medical odyssey, this time into the bonds of matrimony. It is a light-hearted comedy of general practice seasoned with a love interest. In this book Richard Gordon appears to be abandoning broad farce for light comedy. The intensely comic situations which made Dr. Gordon's earlier books so suitable for the films are not so abundant in this latest novel. Even the hero of the novel appears to

be going through that sobering and maturing process that all young doctors undergo. Only the irrepressible Grimsdyke, evidently the author's favourite character, continues in his unethical and breezy way. After the earnest contributions outlining the horrors of Britain's National Health Service, Dr. Gordon's book will be enjoyed as an easily digested demulcent.

NOMINA ANATOMICA: A Comparative Survey of the Basle, Jena, and Paris Nomenclatures. F. Kopsch. 155 pp. Georg Thieme Verlag, Stuttgart; Intercontinental Medical Book Corporation, New York, 1957. $1.55.

About 20 years ago, dissatisfaction with the Basle terminology in anatomy led to the establishment of the Birmingham nomenclature in England and the Jena nomenclature in Germany. The late Berlin anatomist, Dr. Kopsch, compiled a comparative list of the terms in the two German nomenclatures, and this list has now been worked over by Dr. Knese and amended to include the new system adopted by the International Congress of Anatomists in Paris in 1955. In this new edition, no less than 5640 terms are listed in the three terminologies. Where the Paris terminology has made a marked change from the older ones, a short note is given to explain the reason for the change. It is hoped that anatomists will now settle for this new terminology, and may even be induced to use it.

ESSENTIALS OF FLUID BALANCE. D. A. K. Black, University of Manchester, England. 127 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $4.50.

This is a well-written and concise account of a complex subject. For anyone who is already a student of fluid balance it is sure to please. For the others, the "essentials" still present a formidable array. Nevertheless this book is much above the average and is highly recommended for those willing to take the time necessary to improve their knowledge in this field. The author's assessment of the value and limitations of both clinical and laboratory data is particularly well done. One gets the feeling early that Dr. Black is very competent in the realm of fluid and electrolyte balance.

BRITISH NATIONAL FORMULARY 1957: Alternative Edition. Based on a Pharmacological Classification. 245 pp. British Medical Association and The Pharmaceutical Press, London; McClelland & Stewart Ltd., Toronto, 1957. $2.00.

The regular edition of the *British National Formulary* has been used for years as a guide to prescribing under the National Health Service. Indeed, most British general practitioners and specialists carry this small book around with them. Those responsible for its publication have now put out an alternative edition, in which preparations are not listed on an alphabetical basis under descriptive headings such as mixtures, tablets and injections, but are arranged according to pharmacological action. Thus, for example, all vasoconstrictor drugs are listed together, and all preparations used in parkinsonism. There are also short notes on their therapeutic use, so as to make the book of considerable value to students and younger practitioners. Obviously, for anyone not working for the National Health Service, this alternative edition is the one to procure. It is cheap and small enough to slip into a pocket and contains many useful items of pharmacological lore.

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DEMOGRAPHIC STUDIES ON CARCINOMA OF THE UTERINE CERVIX IN SWEDEN (Acta Radiologica Suppl. 145). O. G. A. Berggren, Gynæcological Department of Radiumhemmet, Stockholm. Translated by Virginia Uhlemann. 147 pp. Illust. Acta Radiologica, Stockholm, 1957. Sw. Kr. 30.00.

Berggren briefly reviews observations that have tended to incriminate certain factors—genetic, parity, diet, trauma, inflammation, hormones, race, religion, socio-economic status, etc.—in the causation of cervical cancer. The observations appear somewhat inconclusive or suggestive of factors of only minor significance. Gagnon's finding of the rarity of cervical cancer in nuns* is perhaps one of the most striking. Since the early 1930's, treatment of this condition in Sweden has been practically confined to "individualized irradiation" which, Berggren says, without citing any evidence, gives "more lasting results and considerably fewer complications" than does surgery. He also says, without citing evidence, "As yet we have no definite means of evaluating the degree of malignancy of a cancer, but experience has proved that the earlier treatment is instituted, the better the prognosis." In recent decades almost all patients with recognized cervical cancer in Sweden have been referred to three special clinics, which in the main provided the data for this study. The geographic distribution and the stage of 1822 cases in the years 1935, 1940, 1945 and 1950 are presented and compared. Avoiding the common error of confusing stage and duration but without any discussion in that regard, Berggren refers to stages I and II as "milder forms" and stages III and IV as "more severe forms". From his study he concludes that (1) the risk of cervical cancer developing is greater in urban than in rural districts in Sweden; (2) "classified milder forms" constitute a larger part of cervical cancer in urban than in rural districts; (3) there has been an irregular increase in cervical cancer in Sweden during the period studied; (4) the increase is only partly attributable to a shift of the female population to urban centres; and (5) there has been a shift to "classified milder forms" and to younger age.

Berggren is apparently persuaded that the differences and changes noted are not attributable to differences in diagnosis and detection. If this is so, the study fairly establishes geographic factors as causally related to cervical cancer. But some further consideration of the possibility of differences in diagnosis and detection would seem indicated.

SEX PERVERSIONS AND SEX CRIMES. James Melvin Reinhardt, University of Nebraska, Lincoln, Nebraska. 340 pp. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $6.25.

This book is a social and cultural study of the sex perversions. It is intended for reading by the general lay population, and those having to do with the legal aspects of sex deviation. It is essentially descriptive, with only the most superficial portrayal of the psychological factors in the etiology. For the general practitioner, psychiatrist, or social worker this is a major defect. The author lays stress on the Pavlovian theory of conditioning. Our experience informs us that theories of conditioning are woefully inadequate to explain the complex psychological matrix of the first years of life, which is so important in determining the adult's psychosexual orientation.

The bulk of the book is taken up with case histories of the most serious types of sexual criminal—the lust murderer, the sadist, and the rapist. The general reader may easily be led to believe that such forms of perversion are the most common, whereas in actual fact they comprise less than 5%. Extremely detailed case histories of such serious criminals are given, some of them excellent. There is, however, a tendency to use such value-charged words as "fiendish" and "revolting", which are out of place in a scientific treatise.

The descriptions of the behaviour of pyromanics, sado-masochists, and child murderers are very detailed and give full play to the subjective feelings of these persons. An example of this is the mutilation murder of the 14-year-old boy by Loeb and Leopold, which is currently the subject of a best-seller, "Compulsion" by Meyer.

Perhaps the most interesting chapter in the book is called "The Homosexual and his World". Few people probably realize the tremendous extent of the problem of homosexuality, and the degree to which homosexuals are organized into groups.

For those who are interested in the etiology of sexual perversion this book has nothing to say. For those who are interested in a description of the social aspects of the problem, and more especially the more lurid and violent aspects, this book is replete with information.

INTERPRETATION OF SCHIZOPHRENIA. S. Arieti, Clinical Associate Professor of Psychiatry, State University of Medicine, New York City. 522 pp. Illust. Robert Brunner, New York, 1955. $6.75.

Professor Arieti is a learned man, and his personality as it emerges from his writing is warm and compassionate. He is aware of the horrible predicament in which his patients find themselves and is keen to relieve their sufferings. He has daily seen many mentally ill people and one does not doubt that he is an excellent psychiatrist. How, then, has he written such an irritating book? The author uses extensive and sometimes tedious case histories to illustrate his views. He is rather indiscriminating in his selection of these case histories; one, for instance, which covers several pages, is that of the dead brother of a patient whom Arieti was treating. He had never seen this boy and the whole history is a second-hand account from the surviving brother, some years after the boy whom Arieti discusses in such detail had died. It is hard to see why this weird and objectionable method should be necessary, for it amounts simply to an imaginative interpretation of fraternal gossip.

Arieti's book has been popular. One can only suppose that this is a symptom of our current puzzlement and bewilderment in our conflict with this massive illness. For those who are interested in the response of a clinician to one of medicine's weightiest challenges, this is an important example of the muddled and disordered thinking which has contributed to our perplexity. For those who are learning psychiatry, or who wish to enlarge their knowledge of schizophrenia while not intending to specialize in it, the reviewer can only repeat Robert Burton's advice about chess, "Not for such as is students".

*Gagnon, F.: *Am. J. Obst. & Gynec.*, 60: 516, 1950.

THE RIDDLE OF STUTTERING. C. S. Bluemel, Mount Airy Sanatorium, Denver, Col. 142 pp. Illust. The Interstate Printers & Publishers, Inc., Danville, Ill., 1957. $3.50.

This book is to be highly recommended if for no other reason than that it fills a lack in the all too voluminous literature concerning stuttering, because it describes very well and quite simply some of the psychoneurotic processes involved in this complex disorder.

Dr. Bluemel has had a distinguished career and made some important contributions to the problem of stuttering in his earlier works which unquestionably affected present-day developments. His latest publication is likely to be received with warmth and affection by at least older workers in the field on the American continent, and in Europe generally. It is a book written by a clinician and a good clinician too. Perhaps for this reason it may not get a very good reception from the majority of speech therapists, on this continent anyway, who have "hung their hats on the scientific peg" but who would do well to listen to "the old man of the tribe", if we may use this term somewhat affectionately to describe Dr. Bluemel.

It is unfortunate perhaps that the author elected to use the term "stammering" for what almost all his colleagues have now agreed to call "stuttering", yet Dr. Bluemel is really quite right in saying that "the word *stammering* is good currency and legal tender outside the speech clinic". However, Bluemel offers a theory that the stammerer (stutterer) is poorly organized in his neuromuscular reactions, and because of this experiences more than average non-fluency in childhood. This he calls unorganized speech and postulates that on the basis of this may develop disorganized speech which constitutes primary stammering (stuttering). Further disorganization results in the numerous developmental phases of secondary stuttering involving concomitant psychoneurotic disturbances. He makes numerous important distinctions, contrary to some authorities, between early normal non-fluency and stuttering.

There are some apparent inconsistencies, not so much in the theory itself as between the theory and his recommended therapeutic practices, and it seems a pity that he apparently does not take advantage of many modern and apparently successful techniques in stuttering therapy which are quite consistent with his theory. While recent research indicates that most secondary stuttering manifestations are learned behaviour, Bluemel's therapy appears to attempt to cope with these factors by advocating abortive or avoidance techniques which, it seems fairly obvious from recent researches, offer only temporary relief and ultimately contribute to rather than diminish the abnormality.

However, to the experienced worker in the field, to the clinician, to the stutterer himself, and to the general medical practitioner, this book is certainly to be recommended if only on the basis that the author emphasizes the theme that "stammering (stuttering) is as much a personality disorder as a speech disorder", although this is not thought of as a simple cause-and-effect relationship, so that the reader should be careful not to conclude that Bluemel is postulating stuttered speech as but a symptom of an underlying neurosis and that removal of the neurosis will automatically dissipate the stuttered speech. He is simply saying that meaningful speech therapy should include psychotherapy and that meaningful psychotherapy in the case of the stutterer must include speech therapy if anything like durable assistance is to be provided for the patient. Unfortunately, however, very often we find most schools of thought emphasizing one aspect to the exclusion of the other.

PHYSIOLOGIC PRINCIPLES OF SURGERY. Edited by Leo M. Zimmerman, Department of Surgery, Chicago Medical School, and Rachmiel Levine, Department of Metabolic and Endocrine Research, Michael Reese Hospital, Chicago, Ill. 988 pp. Illust. W. B. Saunders Company, Philadelphia and London, 1957. $15.00.

This book of almost 1000 pages is well bound on good-quality paper, and of attractive format. The different sections are written by 50 individuals with a special interest in the subject considered. Good reference lists are found at the end of each section. The coverage of the different surgical fields is good and the general calibre of the contributions is high.

All the various systems of the body are considered individually and there are also chapters on the more generalized physiological fields relating to surgery such as body fluids and electrolytes, nutrition in surgery, and hæmorrhage and shock.

This book is unhesitatingly recommended as a valuable contribution in this field, which in the past has tended to be overlooked. It is particularly recommended for those studying for higher surgical degrees and also as a reference book for practising surgeons.

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PERIPHERAL NERVE REGENERATION: A FOLLOW-UP STUDY OF 3656 WORLD WAR II INJURIES. Edited by Barnes Woodhall, Professor of Neurosurgery, Duke University Medical School, Durham, North Carolina; and Gilbert W. Beebe, Statistician, Follow-up Agency, Division of Medical Sciences, National Research Council, Washington, D.C. 671 pp. Illust. Superintendent of Documents, U.S. Government Printing Office, Washington 25, D.C., 1956.

One of the best records ever to come out of military medicine is contained in this monograph, which describes a follow-up study of 3656 World War II peripheral nerve injuries. The cases followed up have been carefully selected and the data meticulously documented by a group of authors all with considerable experience in this field and under the editorship of an outstanding neurosurgeon, Dr. Woodhall, and Dr. Beebe, Statistician in the Division of Medical Sciences of the National Research Council.

The book presents a continuity rarely attained in a group project. There are multiple tables somewhat difficult to assimilate, but the text clarifies and summarizes many of the pertinent conclusions from these. All aspects of peripheral nerve injury management are covered: diagnosis, types of repair and the results expected. As a manual of military surgery it is without parallel, and many of the conclusions and findings have civilian application. The presentation is from the standpoint of the neurosurgeon chiefly because assessment or description of the orthopædic problems associated in reconstruction is beyond its scope. As a careful chronicle of the results of peripheral nerve surgery, it is the best that has been written.

DIE PNEUMOLYSE (Pneumolysis). Harald Malluche, Königstein. 292 pp. Illust. Georg Thieme, Leipzig, 1957. D.M. 39.70.

In this monograph the author advocates the wider use of extrapleural pneumothorax in the treatment of pulmonary tuberculosis. Based on reports from the literature and his own experience with this operation on over 400 patients, he discusses in detail the indications, technique, complications and results of this form of treatment. Contrary to the opinion of most specialists on this continent, the author states that collapse therapy has a definite place in the treatment of tuberculosis and that an extrapleural pneumothorax is in many instances superior to other collapse procedures.

He also states that medical treatment should not replace collapse therapy and sees the main significance of drug therapy in the fact that it widens the indications for surgical treatment and improves its results. He advocates no longer than 3-4 months of preoperative therapy, using INH, PAS and thiosemicarbazone, leaving streptomycin in reserve for postoperative complications. His indications for resections are only very few: bronchial stenosis, tension cavities, tuberculoma and lower lobe cavities.

Unfortunately, the results of pneumolysis given are very incomplete. Even if the figures for sputum conversion and disappearance of cavities are high, no information is given on the duration of treatment, the number of unexpandable lungs and complementary operations.

An extensive bibliography on the subject is given. Print and illustrations are of excellent quality.

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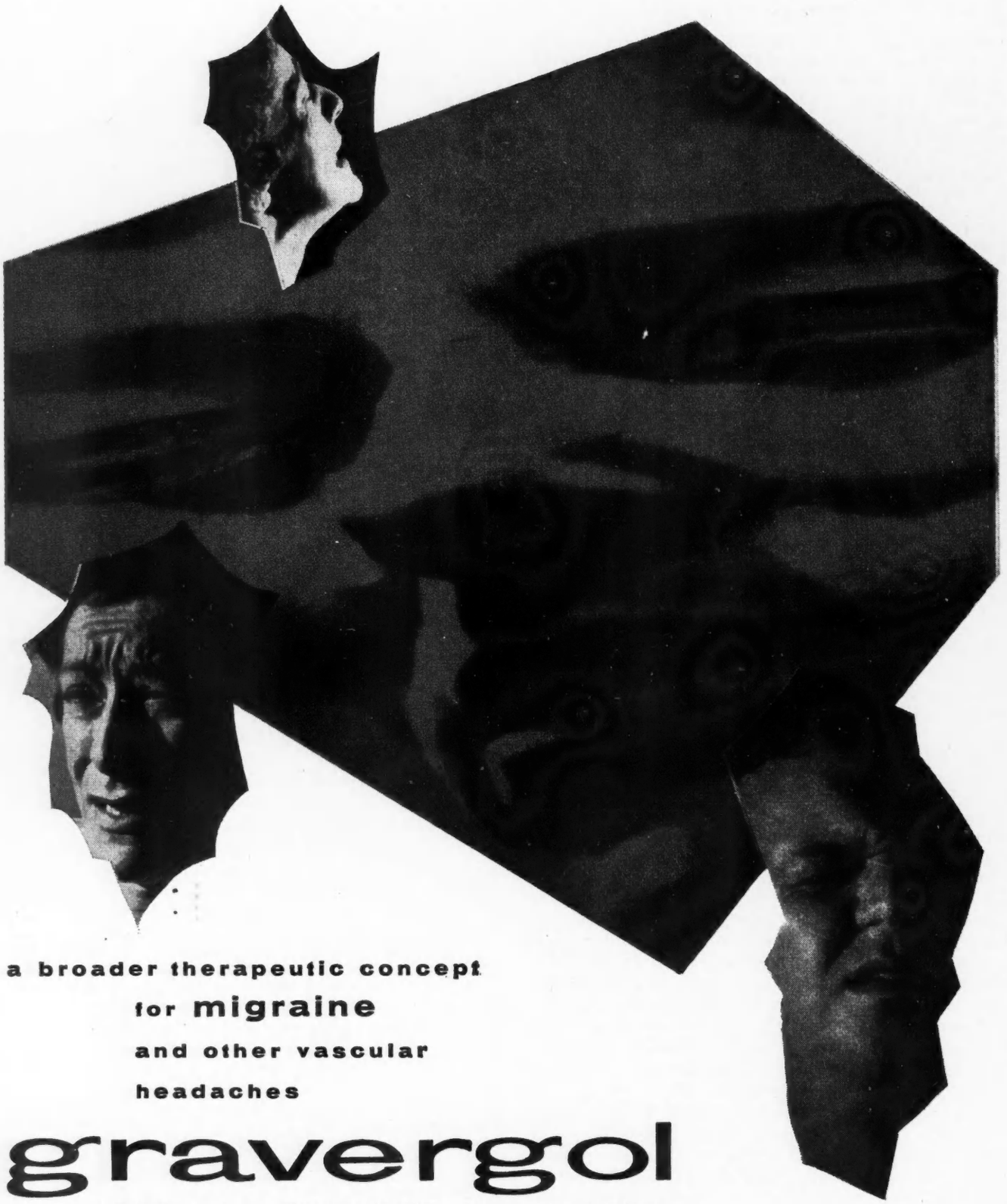

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TOLBUTAMIDE AND DIABETES

Hurwitz and McCuistion recently carried out a double-blind study using tolbutamide and a placebo on a group of 32 diabetic patients. Some of the patients were followed through four periods—two weeks on the usual dose of insulin, two weeks off insulin, two weeks on placebo or tolbutamide, or two weeks on tolbutamide and placebo. The results indicated that in 26 of the 32 patients (81%) control was improved on tolbutamide as compared to the placebo period. In the remaining six no discernible difference between the two drugs was seen. An interesting and not unimportant corollary of this experiment lies in the fact that seven patients or 22% of the group were in good control on placebo. Moreover, eight of a group of 14 patients who had been placed on placebo immediately after two weeks off insulin and before being given tolbutamide showed an improvement in blood sugar values, so that the average fall in blood sugar after a week in these circumstances was 5.9%. This statistically insignificant drop was not maintained during the second week on placebo. The authors conclude that tolbutamide is safe for administration to ambulatory patients if some precautions and close observations are made. Moreover, the mild and temporary drop in blood sugar in the group of patients placed on placebo is a fact that cannot be ignored in short term experiments for the purpose of testing new anti-diabetic agents—*New England J. Med.*, 257: 931, 1957.

PSYCHOPATHS

An editorial writer in the *British Medical Journal* (2: 1546, 1957) objects to the term "psychopath" or "psychopathic patient". He is moved to this objection by the report of a Royal Commission on Mental Illness which appeared in the United Kingdom in 1957, and in which the Commission proposed to recognize three main groups of patients: (a) those suffering from mental illness, (b) psychopathic patients or patients with psychopathic personality, and (c) those of severely subnormal personality, including idiots and imbeciles. Group (b) was to include any type of aggressive and inadequate personality not falling in either of the two other groups and requiring care and treatment. The editorial writer points out that although there is general agreement about the need for such a category as this, which would include alcoholics and other addicts in need of care and treatment, the terminology has caused uneasiness in view of the controversy surrounding it. The trouble is that the term is associated in the minds of many of the general public, as well as the police and legal profession, as defining an aggressive, anti-social member of the community with criminal propensities. Since many patients in the proposed Group (b) have no criminal record, much distress and misunderstanding might be caused by the use of the term.

HÆMATOLOGY IN THE U.S.S.R.

In a recent article in *Klinitcheskaya Meditsina* (No. 7: 6, 1957), Yanovskii summarizes the thinking and aehievements of Russian hæmatologists in the past 40 years. He states that before 1917 there were no real hæmatologists in Russia, though Filatov had described glandular fever (named after him in Russia) and Rustichkyi multiple myeloma (now Rustichkyi's disease in Russia). The Romanowsky stain for blood smears had also come from Russia, as well as Maximov's unitary theory of development of blood cells (1907).

There are now no less than 18 Russian textbooks of hæmatology and some 50 monographs on various problems in this field; 34 yearbooks have been devoted to blood transfusion and related problems. The orthodox unitarian theory of Maximov and the dualistic theory both were found unsatisfactory by Soviet authors. Kriukov is among the founders of the so-called modified unitarian theory. His monograph, published in 1930, remains to this day the best handbook of blood morphology. Whereas abroad the two competing theories were of single origin (extreme unitarian) and of three distinct origins of blood cells, in Soviet Russia there has been general and unanimous acceptance of the modified unitarian theory, with minor qualifications. This has enabled Soviet scientists to branch out into studies of physiology of blood formation, and quantitative and qualitative changes of blood-forming organs in various diseases. Thanks to the suggestion of Arinkin (1927), sternal marrow puncture was introduced into hæmatology. It soon gained world-wide acceptance both as a scientific and as a clinical tool, and its significance in furthering hæmatology and medicine in general can hardly be exaggerated. It gave new impetus to the study of liver, spleen, tumours and particularly lymph nodes by biopsy. Paralleling the study of hæmopoiesis a deeper study of blood destruction and the relationships and regulation of these processes in health and disease developed. It began in Lang's clinic in 1923-24. With his coworkers he formulated the idea that hæmatology is the study of the "blood system" which consists of many functional parts. Their interrelationship constitutes "functional hæmatology". Thus Lang showed the way for development of present trends in Soviet hæmatology and is its founder.

In the field of anæmias, Kriukov demonstrated in 1922 the megalo-

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blastic type of anæmia in sprue. The complicated pathogenesis of hæmolytic anæmias is being studied immunologically; the acquired forms are considered to have an infectious-allergic basis, while other forms are due to toxic influences. A classification of anæmias based on functional disturbances was put forth by Arinkin, Vlados and Duljcin; Sherman produced an etiologic classification and Yanovski a pathogenetic one.

The neoplastic origin of leukæmias has been most widely accepted in Russia. As with other neoplasms, a virus theory was developed by Zilber and Parnes; virus-like bodies have been isolated in leukæmias by the latter. This has of course not solved the problem and will require further study.

Essential agranulocytosis and aleukæmia have been widely studied and are of great interest. "Alimentary-toxic aleukæmia" is a disease first described in the U.S.S.R. It was found to be caused by eating grain affected by a toxic fungus—*Fusarium sporotrichoides*.

The present trend in world literature of so-called immuno-hæmatology was preceded by publications in the U.S.S.R. as far back as 1935. Yanovskii published two papers in 1935 dealing with the presence of hæmolysins in hæmolytic jaundice, and expressed the opinion that all hæmolytic jaundices result from the production of auto-immune antibodies, which become attached to the erythrocytes. This idea with modifications was further elaborated throughout the years and is described in Yanovskii's *Handbook of hæmatology* (1951) and *The blood picture and its clinical significance* (1957). It has been widely accepted in the U.S.S.R.

As abroad, so in the U.S.S.R. the role of the autonomic nervous system in the control of blood formation has received intensive study. Both peripheral and central influences are being investigated.

In re-examining questions of physiology and pathology from the point of view of Pavlov's teachings, regulation of blood composition by the cerebral cortex has received particular attention. This line of study is almost entirely confined to the U.S.S.R. Contrary to the tendency abroad to look for special centres for erythropoiesis, leukopoiesis and thrombocytopoiesis, most Soviet workers hold the view that regulation of the composition of blood is subject to the general laws of reflex regulation.

INTERNATIONAL SOCIETY OF INTERNAL MEDICINE

The International Society of Internal Medicine is holding its fifth congress in Philadelphia, April 23-26, 1958, and the preliminary program is now available. The Society was organized in 1948 in the belief that the tendency to narrow specialization could be counteracted by bringing younger internists together from time to time on an international basis. There will be three morning plenary sessions: among subjects to be discussed are cardiovascular lesions now amenable to surgery, use of anticoagulants, physical medicine and rehabilitation, arthritis, oral antidiabetic agents, and diagnostic and therapeutic application of radioactive agents. The six after-

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noon sessions will be devoted to panels, symposia and brief reports on controversial subjects. Facilities will be available for visiting Philadelphia hospitals and other medical institutions. Official languages will be English, Spanish, French and German, and simultaneous translations will be available for most sessions. Participants in the scientific program will come both from the western countries and those of eastern Europe.

This meeting will be closely followed by the annual session of the American College of Physicians at Atlantic City, April 28-May 2, The Society of Clinical Investigation at Atlantic City, May 4, the Association of American Physicians at Atlantic City, May 5 and 6, and the World Congress of Gastroenterology in Washington, May 25-29. Further information about the congress may be obtained from the Secretary-General, Mr. E. R. Loveland, 4200 Pine Street, Philadelphia 4.

MEDICAL CARE NEEDS AND SERVICES IN THE BOSTON METROPOLITAN AREA

Another in the series of reports on the evaluation of medical care in Boston has been issued by United Community Services of Metropolitan Boston. For the present report, which was prepared by Leonard Rosenfeld and others, a sample of 1208 families, selected by sound statistical procedures, were interviewed by social science students. A list of symptoms was presented to respondents, and if they did not consult a physician for these symptoms it was assumed that this was an unmet need for medical care. One wonders whether this is a valid assumption. In spite of expense, it seems essential that medical examinations of population samples should be undertaken in such surveys, as one has the impression (purely personal, of course) that symptom surveys paint a picture which is far too black. The physician is the only person who can really decide whether the patient is ill. Methods are well described in this report, but one hopes that the authors will move beyond studies of symptoms.

WORLD CONGRESS OF GASTROENTEROLOGY

The host organization, the American Gastroenterological Association, announces further details of its program for the World Congress of Gastroenterology, to be held at the Sheraton-Park Hotel, Washington, D. C., May 25-31, 1958. The main symposia are on peptic ulcer, intestinal infections and infestations, malabsorption, nutrition and its effect on the liver and pancreas (participation from Dr. C. H. Best of Toronto), and gastric carcinoma. In addition over 150 papers have been accepted for presentation. There are 200 names on the program, 36 from the United States and the remainder from 43 other countries, and as of January 1958 over 750 people have registered. Simultaneous translation will be available in German, Spanish, French and English. Social activities and a special program for wives and families have been arranged. The American Gastroenterological Association will have its annual scientific meeting im-

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mediately after the Congress on May 30 and 31. The American Gastroscopic Society will meet on May 24, the Gastroenterology Research Group on May 29 and the American Association for the Study of Liver Diseases on May 31. Information on the Congress from Dr. H. Marvin Pollard, Secretary-General, World Congress of Gastroenterology, University Hospital, Ann Arbor, Michigan, U.S.A.

PROGRESS IN ANÆSTHESIA

The January 1958 issue of the *British Medical Bulletin* (Vol. 14, No. 1) is entirely devoted to anæsthesia. The symposium is edited by Dr. Roland Woolmer, Director of the recently established Research Department of Anæsthetics in the Royal College of Surgeons of England, and contains 16 contributions on various aspects of anæsthesia. These range from the more basic contributions, such as effects of anæsthetics on mechanical receptors and biochemical disturbances associated with anæsthesia, through reviews of recent advances (recent developments in muscle relaxants, anæsthesia for obstetrics, neonatal anæsthesia) to discussions of controversial issues. Thus two contributors have outlined respectively the advantages and disadvantages of controlled hypotension in surgery.

In his introduction, Dr. John Gillies points out that these papers reflect the recent growth of collaboration between anæsthetists and workers in the basic medical sciences and in physics. Thus the symposium will be extremely valuable not only to anæsthetists, but also to surgeons, physiologists, and pharmacologists.

BACTERIOLOGICAL SWABS IN PERTUSSIS

Every practitioner is aware of the difficulties of making a diagnosis of pertussis early when isolation may prove of value and antibiotics influence the course of the disease. Bacteriological evidence is often required to establish the difference between a bout of unspecific bronchitis and pertussis in the preparoxysmal stage, and the various methods of securing bacteriological specimens differ considerably in their yields. A comparative study of the efficiency of methods of swabbing in such cases has been carried out by A. Bogdan of the University of Leeds (*Arch. Dis. Childhood,* 32: 450, 1957). Two methods proved particularly successful. For the supralaryngeal swab technique a straight swab made preferably of wire is used. With the child sitting on his mother's lap, his head kept well back, the swab is held directly above the lumen or upper end of the pharynx, the tongue is depressed by a spatula and the child is asked to cough. Freshly expectorated portions of mucus from the larynx can thus be obtained. This manœuvre in itself is often sufficient to precipitate coughing; if the child does not or cannot cough, a diagnosis of pertussis is unlikely in the face of such insensitivity of the throat.

A pernasal swab may be inserted in the nasopharynx before the supralaryngeal one has been taken and withdrawn afterwards. It is thus exposed long enough to become well contaminated.

A positive culture on diamine-penicillin-fluoride selective medium was obtained in 55% of the cases with supralaryngeal swabs and in 72% with pernasal swabs. Between them, these two techniques confirmed the diagnosis in 84% of the known cases.

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INTERNATIONAL SEMINAR ON HEALTH EDUCATION

The Central Council for Health Education announces an international seminar on health education which will be held in London, England, from April 22 to 25, 1958. It is intended for medical officers and health educators, nurses, teachers, social workers and others. The program will be devoted to health education problems and needs, and is designed to help participants to carry out an effective scheme of community health education in their own fields. Attention will be devoted to basic concepts and principles of health education, to methods and techniques and the integrated use of educational material. Tuition and residence are offered for the modest sum of ten guineas (approximately $29.00) and further information may be obtained from Central Council for Health Education, Tavistock House North, Tavistock Square, London, W.C.1.

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NATIONAL HEART FOUNDATION

The National Heart Foundation of Canada announces that His Excellency the Right Honourable Vincent Massey has graciously extended his patronage to it. This news came just before the opening of the first nationwide canvass carried out by the Heart Foundation on behalf of continuing research and education in cardiology. In preparation for this, much organizational activity has gone on throughout Canada. Exceptional headway has been made in the Atlantic Provinces where committees are now active in Nova Scotia, New Brunswick and Newfoundland. In this nationwide campaign the National Heart Foundation hopes to raise $850,000.

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ADMISSION OF CHILDREN TO HOSPITAL

The Children's Hospital, Columbus, Ohio, has recently published two interesting little booklets for the information of parents and children on hospital admission. The smaller of the two is addressed to parents of children requiring hospital admission, and is entitled "For Mother and Dad". It tells the parents things they require to know about the procedure of admission, and has sections on accommodation available, financing of hospital care and other useful items. The larger book entitled "The Time Dede Went to the Hospital" is well put together and well illustrated. It tells the story of a little girl's adventures in a children's hospital from admission to discharge. Administrators of children's hospitals will be interested in these two booklets.

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BENGER PRIZES TO GENERAL PRACTITIONERS

Prizes for original observations in general practice are awarded each year by Benger Laboratories. Presentation of the first prize will

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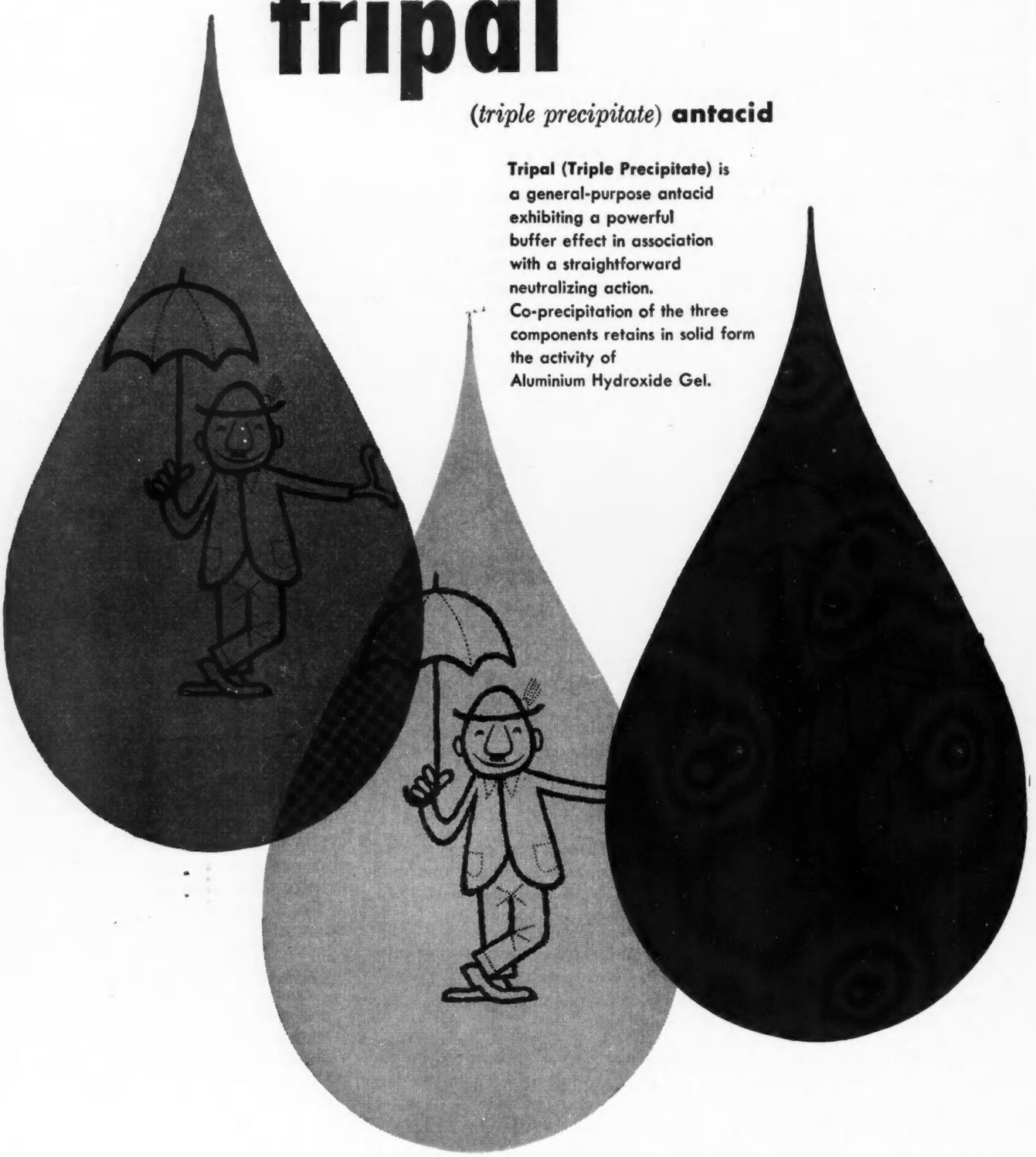

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take place this year in Montreal on March 6. The ceremony starting at 3:00 p.m. will be held simultaneously with a similar one in London, England, at which second and third awards will be made. Speeches and papers selected will be heard on both sides of the Atlantic through a two-way telephonic connection. All general practitioners who wish to attend the ceremony should apply immediately for an official invitation by writing to: The Manager, Benger Laboratories Ltd., 20 Spadina Road, Toronto 4, Ont.

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COMMONWEALTH CHEST CONFERENCE

The Fifth NAPT Commonwealth Chest Conference is announced to be held in London, England, from July 1 to 4, 1958. Representatives will be attending not only from Commonwealth countries but also from many other parts of the world. The provisional list of subjects for discussion includes the following: The world anti-tuberculosis campaign, is it succeeding? danger of TB infection to personnel in pathological laboratories; towards the elimination of tuberculosis from Britain; tuberculosis and leprosy; respiratory disease—a malady of environment; the management of the heart in chronic respiratory disease; tuberculosis medical and social services in the British Commonwealth; the heart patient in every-day life; fungus disease of the lung; the significance of tuberculosis and pneumoconiosis; the relation between tuberculosis and sarcoidosis; personality and tuberculosis; the family and the patient with chest disease; thoracic surgery in pulmonary tuberculosis; the problem of lung cancer.

Further information from the National Association for Prevention of Tuberculosis, Tavistock House North, Tavistock Square, London, W.C.1, England.

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THIRD INTERNATIONAL CONGRESS OF ALLERGY

The Third International Congress of Allergy, sponsored by the International Association of Allergology and the French Allergy Association, will be held in Paris from October 19 to 26, 1958. The program will include symposia on asthma and emphysema, immunology, recent clinical advances, biochemical aspects, auto-immune reactions, dermatology and socio-economic aspects. The participants are world authorities in special fields: Pasteur Vallery-Radot, Löffler, Grabar, Dixon, Chase, Coombs, Forsham, Sir Henry Dale, Halpern, Schild, Harrington, Ackroyd, Dausset, Zondek, Sulzberger, Jadassohn and many others. In addition to the symposia there will be section meetings and round table conferences. An attractive social program is being planned and interesting tours can be arranged before and after the Congress. For
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information regarding program and papers, write to Dr. Samuel M. Feinberg, 303 East Chicago Avenue, Chicago 11, Ill., U.S.A.; and for Congress information and registration, to Dr. Bernard N. Halpern, 197 Boulevard St. Germain, Paris 7, France.

EVALUATION OF NEEDLE NECROPSIES

Findings by needle necropsy are reported by West and Chomet (*Am. J. M. Sc.*, 234: 554, 1957) in 63 cases, of which 50 were checked by complete necropsy. Needle necropsy is of value when permission for a complete necropsy cannot be obtained. (A written consent, however, should be obtained for the performance of a needle necropsy.) Comparison of the results of needle and complete necropsies of the same patients revealed discrepancies in 52%. This demonstrates the limitations of this procedure. Inadequate diagnoses may result because the involved organ or site is not accessible to the needle or because a specimen from these areas may not be representative of the entire organ or system. Also the sample obtained may be inadequate because this is a "blind" procedure.

Diseases which involve organs like the liver, kidneys, and lungs and which produce palpable masses are more amenable to diagnosis by the needle necropsy technique. In disease of these organs, the correct diagnosis was made in each instance where adequate specimens were obtained. In addition to substantiation of the clinical impression, the needle necropsy can provide diagnoses not suspected clinically.

CURRENT STATUS AND TREATMENT OF LYMPHATIC TUBERCULOSIS

On the basis of the experience with patients with lymph node tuberculosis Schless and Wier (*Am. Rev. Tuberc.*, 76: 811, 1957) believe that lymphatic tuberculosis is just one facet of a generalized systemic disease and should be treated as such. It is not a separate or distinct entity. A relatively high incidence of mediastinal lymph node involvement and a very low incidence of mesenteric nodal involvement were noted in this series. This seems to indicate the increasing importance of primary pulmonary tuberculosis in the adult and the decreasing significance of the gastro-intestinal tract as a portal of entry for primary infection, as well as the declining importance of gastro-intestinal tuberculosis in general.

All cases of lymphatic tuberculosis should receive adequate chemotherapy. Multiple-drug regimens, including isoniazid, should be employed in all cases and continued at least to the point of apparent inactivity of the disease. Currently, treatment for 18 to 24 months would be the procedure of choice. There seems to be no great difference in results obtained with isoniazid-PAS or isoniazid-streptomycin regimens.

Except for diagnostic biopsy, which should be done in all cases (if possible), surgery plays a relatively minor role in the modern management of lymphatic tuberculosis. It continues to be indicated

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for removal of fluctuant nodes with imminent danger of rupture and for the correction of significant secondary residuals, such as symptomatic atelectatic or bronchiectatic lung areas after adequate chemotherapy.

The prognosis of adequately treated lymph node tuberculosis today appears excellent, with a very low relapse rate and an excellent outlook with respect to return to a normal useful existence within a relatively short period of time.

TETRALOGY OF FALLOT: CLINICAL HÆMODYNAMIC SPECTRUM OF COMBINED PULMONARY STENOSIS AND VENTRICULAR SEPTAL DEFECT

The tetralogy of Fallot is the most common cyanotic congenital cardiac defect compatible with the maintenance of life beyond infancy and early childhood. It was the first cyanotic congenital lesion amenable to the furtherance of life expectancy by operative intervention. Interest in this lesion was also the main stimulus for the development of our present fund of knowledge relative to congenital cardiac defects. However, because of this early experience with the classic tetralogy and the so-called "blue baby operation," we have in general come to consider that the patient with tetralogy of Fallot must be cyanotic and markedly incapacitated. Otherwise, the diagnosis of tetralogy of Fallot is not seriously entertained.

The considerable body of clinical and physiologic data accumulated over the past 15 years now indicates that the original concept of the lesion as a single, fairly narrowly limited entity is no longer valid. The tetralogy of Fallot can now be demonstrated to occupy a broad spectrum in the field of congenital cardiac anomalies, presenting in widely varying forms. While the entity has been termed a tetralogy, it is becoming apparent that only two features, namely, the pulmonary stenosis and the ventricular septal defect, are essential in the determination of the clinical and physiologic patterns of this defect. Thus, certainly the right ventricular hypertrophy, one of the classic components of the tetralogy, is a purely secondary phenomenon and can be dismissed as a significant factor in the determination of the clinical picture. The role of dextroposition of the aortic root is more difficult to assess and possibly not so easily dismissed. However, clinical and physiologic evidence together with the findings at operation in these patients suggests that the dextroposition of the aorta is of functional origin and not anatomic.

In the presence of large ventricular septal defects, the anatomic relationship of the aorta to the membranous portion of the septum is such that overriding may occur, even though the aorta arises in an entirely normal position from the left ventricle. Thus, in the tetralogy of Fallot, if the ventricu-

lar septal defect is closed, there usually is no technical difficulty relative to the position of the aorta.

It is the size of the ventricular defect and the degree of the pulmonary stenosis and the varying combinations of severity of these two defects that are responsible for the clinical and physiologic findings. The classical tetralogy has a moderately sized ventricular septal defect and a moderate to severe pulmonary stenosis, resulting in relatively equal pressures in the two ventricles, a decreased pulmonary blood flow, and a predominantly right-to-left shunt. However, the patient with the tetralogy of Fallot may be acyanotic and relatively asymptomatic, and masquerade as a patient with an isolated pulmonary stenosis. The pulmonary stenosis is marked and the ventricular septal defect small, resulting in a pressure within the right ventricle greatly exceeding that within the left ventricle. There will be a minimal right-to-left shunt and no left-to-right shunt.

The other end of the spectrum also reveals an acyanotic patient with almost full activity. This patient has a large ventricular septal defect and a very mild infundibular stenosis with a resulting large left-to-right shunt and no right-to-left shunt. The pressure in the right ventricle may be equal to or less than that within the left ventricle. Pulmonary hypertension may exist and the systolic pressure gradient between the pulmonary artery and right ventricle may be minimal. This patient is usually thought to have a large ventricular septal defect, and the diagnosis of tetralogy of Fallot is not considered.

It is probable that for a better understanding of the clinical and hæmodynamic features of this anomaly the term "tetralogy of Fallot" should be discarded. However, it is certain that it will disappear from our terminology only slowly and with great reluctance.—M. C. McCord *et al.: Circulation*, 16: 736, 1957.

LONG-TERM FOLLOW-UP OF PATIENTS WITH HEALED BACTERIAL ENDOCARDITIS

The present status of 17 patients who were discharged from hospital cured of bacterial endocarditis six or more years ago is detailed by Hall (*Ann. Int. Med.*, 47: 880, 1957). During the first year after penicillin therapy five patients died, three of congestive heart failure and two of noncardiac causes. Two additional patients died 26 months and six years after penicillin therapy, of coronary heart disease and congestive failure respectively.

Of 10 living patients followed up for from six to 10 years, four are asymptomatic, five have slight limitation of activity, and one is moderately disabled. Four of the seven patients with aortic regurgitation are now dead, and the other three have shown a decrease in functional capacity. This finding contrasts with that for nine patients who had only mitral valve

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disease, of whom two are dead, three have worsened symptomatically, and four are unchanged.

This study shows that some patients may remain well for from six to 10 years after recovery from bacterial endocarditis, especially if aortic regurgitation is not present. It also indicates that healed bacterial endocarditis must now be considered in the differential diagnosis of mitral regurgitation and of aortic regurgitation.

CZECHOSLOVAKIA BACK IN WHO

Czechoslovakia has resumed active participation in the work of the World Health Organization (WHO). Czechoslovakia became a member state of WHO in March 1948, but in April 1950 discontinued active participation in the organization. During 1957, Albania, Bulgaria, Poland, the USSR and Rumania announced their resumption of active participation in WHO; Hungary, the Ukrainian SSR and Byelorussian SSR remain inactive.

ANTICOAGULANTS AND CEREBRAL INFARCTION

More light has been thrown on the problem of therapy in cerebral infarction by members of the Department of Medicine of Western Reserve University School of Medicine, Cleveland, Ohio. Experimental cerebral infarcts were produced in 36 dogs by the injection of fragments of homologous clots into their carotid system. Whereas several animals suffering from grossly hæmorrhagic lesions survived and even reached a certain degree of clinical improvement in the untreated series, four of the 12 animals surviving infarction more than 24 hours in the dicoumarol treated group died after institution of therapy. In two cases, the prothrombin time was not prolonged beyond the degree to which it is purposely altered in clinical practice. Five of the surviving animals in the treated group had sustained anæmic infarcts, which may account for their survival. The authors conclude that "these findings are interpreted as providing confirmatory evidence for the belief of many clinicians that anticoagulant drugs are contraindicated after recent embolic cerebral infarction in humans."—*Am. J. M. Sc.*, 234: 663, 1957.

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COMPARATIVE POTENCY OF RECENTLY DEVELOPED ORAL DIURETICS

Members of the Department of Pharmacology and Medicine of Baylor University College of Medicine have recently undertaken to compare the potency of a few synthetic orally active non-mercurial diuretic agents commercially available. These belong to the group of pyrimadine derivatives. The comparison was based on the extent to which they produce a rise in sodium excretion. These compounds included aminophylline, aminoisometradine (Rolicton), and aminometradine (Mictine). They were first tried on dogs, both hydrated and non-hydrated, and animal experimentation was followed by clinical assessment in male patients suffering from roughly equivalent degrees of well-controlled congestive heart failure. These men were kept on an intake of 50 mEq. of sodium and 3 litres of water per 24 hours. Each drug was first tested in increasing dos-

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ages until signs of toxicity appeared; the optimum response was then determined. Using the response obtained from the intramuscular administration of 1 ml. of meralluride (Mercuhydrin) as a standard of 1.0, it was found that 1200 mg. of aminophylline administered orally produced gastro-intestinal symptoms in over 25% of the patients and compared at 0.5 or less with meralluride. The action was both prompt and of short duration, the maximum taking place in the first two hours after administration, and producing an excretion of sodium and chloride reaching a level of nine times the control while at its peak. Oral aminoisometradine in a dosage of 800 mg. produced a peak action between 6 and 12 hours and rated at about 0.5 as compared with meralluride. Aminometradine in a dose of 600 mg. was slightly more active, giving a comparison quotient of 0.7 (856 mg. being theoretically equivalent to 1 c.c. of intramuscular meralluride).

In the course of their animal experimentation the authors failed to notice any alteration in glomerular filtration rate with any of the three drugs. All of them had similar effects on the renal-transport mechanism, producing an increased excretion of sodium and chloride and a slight inhibition in the excretion of ammonia and phosphate.—*Am. J. M. Sc.*, 234: 640, 1957.

AERO MEDICAL ASSOCIATION

The Annual Meeting of the Aero Medical Association will be held in the Statler Hotel, Washington, D.C., March 24-26, 1958. The program reflects the fact that research has led at last to the threshold of manned space flight. Specialists will review studies of human responses to weightlessness, the vacuum of space, and cosmic radiation. More general interests will receive special emphasis. There will be sessions on acceleration, oxygen equipment hypoxia and hyperoxia, human behaviour, sensory problems, hyperthermic and hypothermic stress, physiology, psychology, civil aviation medicine, and clinical problems. The program has been made sufficiently broad to serve all interests and arranged in three simultaneous sessions so that each participant can select the material which suits his special interests. The Louis H. Bauer Lecture will be given by Dr. Rodolfo Margaria, Professor of Physiology and Biochemistry at the University of Milan.

Information from the Aero Medical Association, P.O. Box 26, Marion, Ohio.

AWARD FOR RESEARCH IN LARYNGOLOGY

The William and Harriet Gould Foundation of Chicago announces an annual award of $250, known as the Gould Award, for outstanding research in otolaryngology. While the award recognizes the completion of a specific research project, favourable attention will be given to investigators with a long-term interest in the subject. Further information from Hans von Leden, M.D., Medical Director, William and Harriet Gould Foundation, 30 North Michigan Avenue, Chicago 2, Illinois.